Modern Nutrition *in* Health *and* Disease

Dietotherapy

Second Edition Edited By

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59 Contributors

75 Illustrations and 154 Tables



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Preface to Second Edition

The appearance of this second edition of Modern Nutrition in Health and Disease within five years of the publication of the first edition is indicative of the rapid advances still being made in the field of nutrition Revision involved many deletions and more additions There are two entirely new sections, one on chemical and other additives to foods, and the other a discussion of dietary factors in the production of atherosclerosis and coronary artery disease The discussion of nutrition and resistance to infection has been divided into two parts (A) Nutrition and Natural Resistance to Infection and (B) Nutrition in Relation to Acquired Immunity, so that the major aspects of the relationship might be more readily comprehended The Canadian Dietary Standards for adults and children are included, as well as the National Research Council's Recommended Daily Dietary Allowances The chapter on Principles of Emergency Feeding has been revised and expanded to include current recommendations on minimal nutritional allowances by both the Office of Civil Defense Mobilization and the Office of the Surgeon General, U S Army We hope that this text will amply fulfill its purpose of bringing to the reader up to date authoritative information on the basic knowledge of nutrition and its application to the practice of medicine

We are deeply grateful to all of the contributors who have thoroughly revised or rewritten their respective chapters in the light of the newer advances in nutrition We also wish to acknowledge our indebtedness to those who have carefully read and constructively criticized certain chapters in this volume Our thanks are due to Mrs Rita D Gnesin for her faithfulness in the arduous secretarial work entailed in the preparation of this volume Finally, we wish to acknowledge our debt to the staff of Lea & Febiger for unfailing courtesy and valuable assistance in bringing the book to press

Michael G Wohl
Robert S Goodhart

Preface to the First Edition

IN THE last decade, the science of nutrition has developed rapidly This book has been undertaken to present the salient advances in nutrition that have a direct bearing on the *maintenance of optimum health and the prevention* and treatment of disease The object of the book is to present an authoritative and up-to-date discussion of every aspect of nutrition and provide the practicing physician and the student of medicine with a sound knowledge of both current advances in and the practical application of that science

The general *organization of the book is similar to* Wohl's *Dietotherapy*, but each chapter has been reconsidered and most of them have been re-written, so that approximately 80 per cent of the text consists of new material The book is divided into three parts Normal Nutrition, Nutrition in Disease and Nutrition in Periods of Physiologic Stress, and the approach throughout has been from the clinical point of view There are entirely new chapters on Body Composition, Hormonal Control of Metabolism, the Physiology and Psychology of Hunger, Antimetabolites, Principles of Dietotherapy, Nutrition in Ophthalmology, and Emergency Feeding

The contributors are authorities in their fields and the material has been integrated so that this book represents a co operative effort The editors are most grateful to the contributors for their thoroughness and for their patience

We wish to acknowledge our indebtedness to those who have carefully read and constructively criticized certain chapters in this volume Our thanks are due to Mrs Clara Wein and Mrs Rita D Gilbert for their faithfulness in the arduous secretarial work entailed in the preparation of this volume Finally, we wish to acknowledge our debt to the staff of Lea & Febiger for unfailing courtesy and valuable assistance in bringing the book to press

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Contents

PART I

NORMAL NUTRITION

Modern Nutrition in Health and Disease

Part I Normal Nutrition

Chapter 1

Body Weight, Body Composition and Calorie Status

By Ancel Keys

THE body is, in the most literal sense, the product of its nutrition. "Man ist was er isst," wrote Goethe. Though the transformations are profound, nutrition begins with the foodstuffs and proceeds to the material end result, the living body and its functions. The most elementary, but certainly not the least important, aspect of nutrition is the gross mass of tissue it produces and maintains. The most obvious and in many populations perhaps the most common nutritional defects are those caused by gross calorie imbalance.

The opposite defects of emaciation and obesity have always been with us and this is true today in all populations. Even in the midst of plenty, starvation caused by disease is common because many illnesses interfere with the appetite or the assimilation of food. In the simplest of societies obesity may be rare, either because of chronic food shortages or because physical exercise is an effective preventive, but as society becomes more specialized, more prosperous and more sedentary, an excessive accumulation of body fat tends to be the rule unless it is consciously combatted.

The first step in nutritional evaluation is a calorie judgment: is the patient too thin or too fat? Mere inspection of the body allows rough classification. In extreme examples, obesity and emaciation are readily recognized, even when the presence of edema or dehydration complicate the picture. But more moderate departures from normality present problems of evaluation and even at the extremes there is the need to determine the degree of abnormality and its response to treatment. Elementary considerations demand biochemical and functional definitions and measurements of obesity, fatness, overweight, underweight, leanness and emaciation. Metabolic analysis, of course, cannot even begin properly without consideration of the gross composition, and its changes, of the body.

Until recently, besides the impressionistic methods of gross inspection and digital feel, only gross body weight, sometimes supplemented with a few measurements of external dimensions, had to suffice for studies on living

man Fortunately, new methods are now at hand for analysis of the body mass into metabolically distinct components [39 61] These, together with the more wide-spread application of statistical methods and concepts, provide increasingly useful and precise norms for guidance in calorie nutrition

The Meaning of Body Weight —The gross body weight, *per se,* has some direct metabolic significance in that it affects the metabolic cost of physical activity Most of the energy cost of physical activity is expended in simply moving the body around With a fixed amount of activity —number, extent, speed and force of movements—energy expenditure tends to be directly proportional to gross body weight [2 35] This not only affects calorie requirements, there is the integral need to provide digestion, respiration and circulation for this metabolism

Actually, grossly overweight persons tend to be relatively inactive, the movements they make are expensive in calories but they make fewer movements than the person of average weight Many recent studies show that overweight persons are not characterized so much by large food consumption as by physical inactivity [3 49] However, when a heavyweight has to move quickly there is an excessive demand for energy and this may mean a strain on one or more vulnerable organs or functions Possibly this contributes to the high mortality rate of overweight persons

Insurance companies report an excessive death rate of overweights from a variety of causes, including accidents A heavy body is an impediment in avoiding many accidents simply because it is harder to move or to change the direction of movement of a heavy body Further, the damaging force in a fall is increased with increasing body weight It should be noted that over 20 percent of all accidental deaths in the United States are caused by falls

Nevertheless, the major importance of the body weight is its association with the body fatness, a fact that explains the common error of considering that overweight and obesity are identical Obesity means excessive fatness and *it is essential to adhere to this definition* [36 39] Athletes are *often* overweight but underfat [3] It is safe to conclude that a middle-aged man who is 30 or more pounds heavier than the average man of the same height is obese, that is overfat But at lesser degrees of overweight the relationship between obesity and overweight is not close, particularly at younger ages [8 9 10]

Many sedentary persons are excessively fat but not overweight, while the opposite condition, overweight without being fat, is common among people doing heavy physical work The two conditions are, in fact, metabolic opposites, the one tending to result from lack of activity, the other from excessive activity Attention to this discrimination discloses differences in circulatory characteristics pertinent to circulation and health [66] Besides such physiological differences between fat persons and overweight persons who are not fat, there are emotional and psychological differences of perhaps even greater significance

Besides differentiation between fat and muscle in the gross body weight, variations in the water content of the body must be considered In ascites 5 to 10 kilograms of fluid in the abdominal cavity may be encountered and much larger totals of edema fluid are not rare One of Simonart's[60] starved

patients lost 20 kilograms in a week while his nutriture was improving and this is by no means unique Extreme edema is readily detected but more moderate variations in hydration are not easily recognizable Clinical recognition of the presence of edema requires an accumulation of the order of 5 to 10 per cent of the total body weight as excess water [39, 41] The variable contribution of water to the total body weight of clinically healthy persons is frequently indicated in the weight fluctuations seen on reducing diets under controlled conditions [5]

Another contributor to confusion about the meaning of the total body weight is the variable weight of the bony skeleton The mineral mass in the adult skeleton averages something like 6 per cent of the normal body weight of the adult but in different persons it may be as low as 4 per cent as or high as 9 per cent [39]

Perhaps a more important contribution of the skeleton to the body weight is through its form Relative body weight and overweight and underweight are commonly computed on the basis of weight for height But a broad and short skeleton automatically means a large body weight per unit of height and so far no system has been devised to allow for this in a practical manner The body "frame types to be discussed below are theoretical concepts devoid of real utility in the absence of agreed methods of measurement and classification

Body Weight Standards —Until lately almost all statistical evaluations of calorie status obesity, emaciation, and gross nutritional health, have been based simply on the gross body weight as related to height In the United States the standard of reference has long been the tables of average weight for height and age originally published by the Association of Life Insurance Medical Directors and the Actuarial Society of America in 1912 under the title "Medico-Actuarial Mortality Investigation" (New York) These tables are still the most widely used and are summarized in Tables 1 and 2

TABLE 1 —GRADED AVERAGE WEIGHT IN POUNDS OF MEN OF DIFFERENT STATURES AT VARIOUS AGES*

Height Inches	Age Years 20	25	30	35	40	45	50	55
60	117	122	126	128	131	133	134	135
62	122	126	130	132	135	137	138	139
64	128	133	136	138	141	143	144	145
66	136	141	144	146	149	151	152	153
68	144	149	152	155	158	160	161	163
70	152	157	161	165	168	170	171	173
72	161	167	172	176	180	182	183	184
74	171	179	184	189	193	195	197	198
76	181	189	196	201	206	209	211	212

* Davenport C B Body Build and Its Inheritance Publication 329, Carnegie Institute of Washington 1923

Elsewhere,[36, 38] we have discussed the limitations of these tables which merely give the average values for men and women of specified ages who

obtained life insurance policies at standard premium rates from 1885 to about 1905, mostly in urban centers on the eastern seaboard. The heights and weights were recorded as for "ordinary clothing", what this means today is questionable. However, for men at least, similar values may apply approximately to the undressed state, that is, in socks and shorts, because the heel height (about 1 inch) roughly counteracts the clothing weight which was customary half a century ago. For women the application is more difficult because of the variability of heel height and the great reduction in female clothing weight over the intervening years.

TABLE 2.—GRADED AVERAGE WEIGHT IN POUNDS OF WOMEN OF DIFFERENT STATURES AT VARIOUS AGES*

Height Inches	Age, Years							
	20	25	30	35	40	45	50	55
56	106	109	112	115	119	122	125	125
58	110	113	116	119	123	126	129	129
60	114	117	120	123	127	130	133	133
62	119	121	124	127	132	135	138	138
64	125	128	131	134	138	141	144	144
66	132	135	138	142	146	149	152	153
68	140	143	146	150	154	157	161	163
70	147	151	154	157	161	164	169	171
72	156	158	161	163	167	171	176	177

* Davenport, C. B. Body Build and Its Inheritance. Publication 329, Carnegie Institute of Washington, 1923.

More recently, tables have come into use which list body weights for the same height under three headings: "light" or "small frame," "medium frame" and "heavy" or "large frame." The medium frame values correspond to the averages in the older tables and the "light" and "heavy frame" weight values are simply some 5 to 8 per cent smaller or larger respectively. This is in recognition of the obvious fact that appropriate weights for the same height must differ according to the skeletal type. Unfortunately, however, there is no accepted system for deciding who has a "light frame" and so on and no actual evaluations of frame size were made in developing the tables.

Apparently the observed frequency distributions of the weight values used for the original tables of 1912 (where frame was not considered) were merely divided into thirds. The lighter third of men of a given height and age were arbitrarily defined as having a "light frame" and the mean weight of this group was then considered to be the average body weight of men of "light frame" of the given height and age. In other words, these tables have no basis in measurement and are useless and misleading except to indicate that a single "average" body weight for given height and age is inadequate and that differences in skeletal type may explain some of the variability observed in clinically healthy persons of t

Still more recently, the Metropolitan Life Insurance Company has pop-
rized the idea, enunciated by Fisher and Fisk [1] that the observed body
ights for the average of the population are not necessarily those most
nducive to health In the United States and many other countries it is
ual for body weight to increase with age long after body length growth is

TABLE 3 —DESIRABLE WEIGHTS FOR MEN*

Height in inches (with shoes on)	*Small frame*	*Medium frame*	*Large frame*
62	116–125	124–133	131–142
63	119–128	127–136	133–144
64	122–132	130–140	137–149
65	126–136	134–144	141–153
66	129–139	137–147	145–157
67	133–143	141–151	149–162
68	136–147	145–156	153–166
69	140–151	149–160	157–170
70	144–155	153–164	161–175
71	148–159	157–168	165–180
72	152–164	161–173	169–185
73	157–169	166–178	174–190
74	163–175	171–184	179–196
75	168–180	176–189	184–202

Weight in pounds according to frame as ordinarily dressed

* From Metropolitan Life Insurance Company Ideal weights for men Metropolitan Life Ins Bull *24*, 6 1943

TABLE 4 —DESIRABLE WEIGHTS FOR WOMEN*

Height in inches (with shoes on)	*Small frame*	*Medium frame*	*Large frame*
59	104–111	110–118	117–127
60	105–113	112–120	119–129
61	107–115	114–122	121–131
62	110–118	117–125	124–135
63	113–121	120–128	127–138
64	116–125	124–132	131–142
65	119–128	127–135	133–145
66	123–132	130–140	138–150
67	126–136	134–144	142–154
68	129–139	137–147	145–158
69	133–143	141–151	149–162
70	136–147	145–155	152–166
71	139–150	148–158	155–169

Weight in pounds according to frame as ordinarily dressed

From Metropolitan Life Insurance Company Ideal weights for women Metropolitan Life Ins Bull, *23* 6 1943

finished But it is possible to argue that the usual gain of weight beyond age twenty-five or thirty is undesirable or at least may be unnecessary Accordingly, tables of "desirable body weight" (at first labelled "ideal") have been provided [49] Tables 3 and 4 specify "frame size," with no more precise definition than indicated above, and they indicate a "desirable

2

range (of 7 to 18 pounds for different frames and heights) within each height and frame class. But age is not specified since the theory is that no weight change with advancing age is desirable. The values are, in fact, merely a re-arrangement of the 1912 tables but limited to persons of twenty-five to thirty years of age.

All of these weight tables have their value, but they have far less validity than is claimed for them. The actual averages and standard deviations for clinically healthy persons of specified age, sex and height in the United States at present are largely unknown, and the further specification of "optimal" or "ideal" weight is still more uncertain. For estimating present averages, without regard to what may be "desirable" values a few data have been obtained from Selective Service records[18] and studies of the *Quartermaster Corps*.[61,57]*

The average white registrant for Selective Service just before World War II was twenty-six years old, and was, unclothed, 68.5 inches tall and weighed 152.2 pounds. From the old 1912 tables a *clothed* weight of 152.0 pounds would be predicted for the average twenty-six year-old man whose height, *in shoes*, is 68.5 inches. Unfortunately, the Selective Service data are not analyzed for other ages and heights and the data for men after several years in the Army differ from those of men when first called up for service. An analysis in 1946 and 1949 of data on men leaving the Army after several years indicated that in both white and Negro men the body weights are higher than would be expected from the 1912 tables.[53] The white separatees averaged 104.4 per cent and the Negro separatees averaged 105.0 per cent of the values listed in the Medico-actuarial tables of 1912.

For women the actual averages for the population are still more uncertain. No samples generally representative of the population have ever been studied. A sample of about 8500 women in the Women's Army Corps and in the Army Nurse Corps averaged 26.9 years old, 63.9 inches tall and 130.9 pounds in body weight, the 1912 tabular weight figure would be 128.5.

A national survey in Canada, covering some 22,000 persons in a carefully selected stratified sample of the entire country, provides more acceptable modern data that may be applicable to the United States as well as to Canada.[58] The average weights for specified heights found in the Canadian survey are given in abbreviated form in Table 5. These weights are for persons in "ordinary" indoor clothing, without shoes."

What then may be concluded about standard, desirable and "ideal" body weights? In the first place, it is obvious that the available data are inadequate to describe the actual weights of "average" members of the population or to specify what weights would be most conducive to health. If anything, the young men of today may be heavier, at the same height, than fifty years ago and this may possibly be true of young women as well. The average body weights of older persons are much more uncertain, though there is no doubt that weight, in the United States, tends to change with age in something like the same manner as at the turn of the century. It is widely believed that this increase in weight is undesirable, but the data have serious shortcomings, unless it is specified that "overweight" is of great degree, say 40 pounds or more in the man of average height. Gross

*New average weight tables were published by the Society of Actuaries in 1959, see Table 135, page 863.

obesity, like extreme emaciation, should certainly be corrected by proper nutrition

Weights and Heights During Growth —The present discussion is primarily concerned with adults and space does not permit detailed consideration of the situation during growth, that is in infants and children Far more data are available on children than on adults Height-weight data for the United States have been summarized recently[30] and Garn and Shamir [7] have reviewed anthropometric methods, including fat estimation in the study of growth

TABLE 5 —AVERAGE WEIGHTS FOR HEIGHT AND AGE OF CANADIANS IN ORDINARY INDOOR CLOTHING WITHOUT SHOES ABBREVIATED AND ADAPTED FROM TABLE 2 OF PETT AND OGILVIE (1956)

Men

Height in inches	*Age in Years* 25	35	45	55	65 and over
60	128	139	136	137	130
62	135	146	144	145	140
64	142	152	152	152	149
66	150	160	161	160	158
68	156	167	169	168	167
70	163	174	177	176	177
72	170	182	186	184	186
74	185	189	194	191	195
Women					
58	113	124	131	137	128
60	118	128	135	142	136
62	123	132	139	146	144
64	128	135	143	151	152
66	133	139	147	156	161
68	138	143	151	160	169
70	143	146	154	165	177

At given age during the growing years both sexes in the United States have been getting taller and heavier during at least the last fifty years Table 6 summarizes averages obtained by Hastings [9] in 1899 in Omaha, Nebraska, and by Stuart and Meredith[65] in Iowa City from 1930 to 1945 The latter weights were measured in the lightest of underclothing and probably are somewhat smaller than would be strictly comparable to Hastings' data of some 40 years earlier

These and other data suggest that in a span of only 40 years rates of growth in both body length and weight increased substantially in the Mid-West At given height, however there seems to have been little change in body weight For example in 1899 the average height for 12-year old boys was 55 2 inches and average weight was 72 6 pounds, in 1930–45 a height of 55 2 inches was the median for 10-year old boys and they had a median weight of 71 9 pounds It might be inferred then that the average body composition did not change over this span of years but this conclusion is not safe, the proportion of fat to muscle could be quite different in the two periods and simple height and weight measurements would not reveal this

Body Weights in Other Countries.—Compared with the United States, information on average and desirable body weights in many, but not all other countries is as deficient, or worse. Older data, often of doubtful statistical merit, are summarized by Krogman.[43] Useful data are available for Great Britain and Japan. There is no doubt that, at the same height and age, Britons tend to be lighter than Americans and the age increment in weight is smaller.[34] In Japan, not only is the relative weight smaller but the age-increment in weight is much smaller than our own.[71]

TABLE 6.—HEIGHTS AND WEIGHTS OF MIDWESTERN CHILDREN IN 1899 (MEANS FROM OMAHA, NEBRASKA) AND IN 1930–45 (MEDIANS FROM IOWA CITY, IOWA). DATA FROM HASTINGS[29] AND STUART AND MEREDITH.[65] HEIGHTS IN INCHES, WEIGHTS IN POUNDS

	Boys				*Girls*			
Age	*Height*		*Weight*		*Height*		*Weight*	
	1899	30–45	1899	30–45	1899	'30–'45	1899	'30–45
5	41.6	43.8	39.3	42.8	41.5	43.2	38.2	41.2
6	43.6	46.3	42.6	48.3	43.2	45.6	40.8	46.5
7	45.6	48.9	46.8	54.1	45.7	48.1	45.6	52.2
8	47.8	52.8	50.9	60.1	47.3	50.4	48.9	58.1
9	49.6	55.0	55.2	66.0	49.7	52.3	51.9	63.8
10	51.6	55.2	61.3	71.9	51.7	54.6	59.9	70.3
11	53.1	56.8	64.9	77.6	53.2	57.0	63.9	78.8
12	55.2	58.9	72.6	84.4	55.5	59.6	72.7	87.6
13	57.1	61.0	78.3	93.0	58.5	61.9	83.5	99.1
14	59.4	64.1	87.4	107.6	60.3	62.8	94.4	108.4
15	62.2	66.1	103.3	120.1	61.8	63.4	102.8	113.5
16	64.4	67.6	116.4	129.7	62.2	63.9	110.8	117.0
17	66.9	68.4	125.0	136.2	62.8	64.0	110.8	119.1
18	67.4	68.7	130.2	139.0	62.9	64.0	110.4	119.9

A continuous rise in body weight with age, such as is the situation in the United States, is not inevitable. Among relatively primitive people on islands in the China Sea, there is no increase of average body weight after twenty-five.[1] It is interesting that most of the usual age-increment in body weight common among adults in the Western World rapidly disappears in populations on short rations who are not actually starving.[39] A relatively moderate reduction in the food supplies available for the entire population tends to produce the greatest loss of body weight in the older, fatter individuals and the health records of World War II suggest that this may be beneficial.

Lean Body Mass Versus Fat-free Body.—Behnke[1] proposed the analysis of the body into two parts, (1) fat and (2) the "lean body mass." The latter was conceived of as the body with the least amount of fat compatible with health and was considered to include 'essential fat' amounting to 10 per cent of its weight. This arbitrary definition was later revised so that the "lean body" was held to include 2 per cent of its weight as fat. Since it

is impossible to decide how much fat is really essential and since no methods are available to separate body fat into essential and non-essential parts, more recent investigations have either re-defined the "lean body mass" as the body devoid of all fat[17] or, better, have abandoned the term and deal with the fat free body and the body fat, the latter being the sum of ether-extractable substances in the body

The Compartments of the Body —Metabolically, the most elementary analysis of the body mass begins with the differentiation between the part of the body that is relatively active in energy metabolism and the relatively

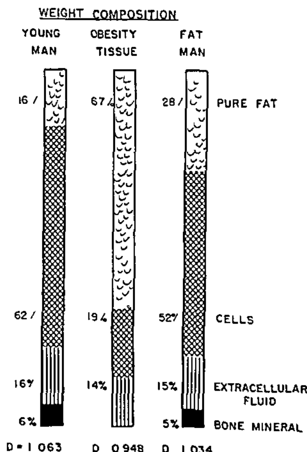


FIG 1 —Body composition from densitometric analysis

non active part In the latter category are the body fat the extracellular fluids the mineral portion of the bony skeleton and a negligible mass in the horny epidermis the nails and the hair[38 61] The body fat tends to be the largest and most variable compartment though the extracellular fluid mass is not small and may be very large in cases of edema

If, from the total mass of the body the relatively non-active masses of fat, extracellular fluid and bone mineral are subtracted, the remainder may be termed the "active tissue mass" This mass primarily cells of course, may represent anything from perhaps 30 to 60 per cent of the total body weight but it accounts for substantially all of the energy consumption The

highest values for cell mass as a percentage of body weight will be found in lean, very muscular men in a state of dehydration, the lowest values will occur in sedentary women who are both fat and edematous

The foregoing subdivision of the mass of the body into these "compartments" is not only metabolically reasonable, it corresponds to some degree, as we shall see, with the availability of practical methods of measurements The diagrams in Figures 1 and 2 illustrate the two systems

It will be observed that these systems pay little attention to the traditional classifications of the body into kinds of parts—bony skeleton, cartilaginous skeleton, voluntary muscle, and so on—or into systems—skeletal system, muscular system, nervous system, and so on *Partly this is be-*

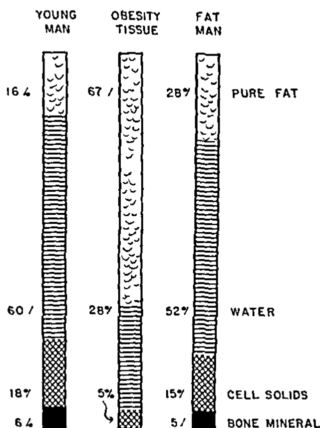


Fig 2 —Body composition from water analysis

cause the first focus is on gross metabolism, equally important however, is the fact that no practical methods are available or even conceivable, currently, to provide reliable measurement of the living human body in these other terms

Furthermore, when the center of interest is nutrition, and especially changes in nutritional state some questions about organs and organ systems, and the relations between them, are of only subordinate interest For example, the mass of the brain and nervous tissue is relatively insensitive to nutritional effects, *at least after growth is finished Mental* and nervous function may be greatly affected, but this is not at all closely related to the mass of the brain and nerves, the mass itself is remarkably

constant in the face of starvation or of gross overnutrition of the body as a whole.[39] How much the adult skeletal mass responds to changes in nutrition is unknown, but in any event the change is relatively small and slow. On the other hand, the masses of some organs and organ systems seem to respond alike to gross nutritional changes. In starvation, the percentage reductions in the masses of the heart, voluntary muscles, kidneys, testes and many other organs are similar.[39]

In Figures 1 and 2 it will be observed that there are no places, as such, for blood, skeleton or adipose tissue. The estimation of total blood volume (and hence its mass) is not difficult and a combination of the dye method (T-1824 dilution) or labelled erythrocyte injection, with a hematocrit measurement, for example, provides estimates of both circulating blood plasma and cells. These measurements are useful and provide additional detail but may not be essential in the first stage of metabolic analysis. The total mass of the blood is not a large part of the total body mass and it accounts for only an infinitesimal part of the total energy metabolism of the body. The plasma, which normally comprises more than half of the blood volume and makes up about 4.0 per cent of the body weight, is included in the calculations of extracellular fluid. The cellular components of the blood account for only about 3.5 per cent of body weight and are included in the "cells" or "cell solids" in Figures 1 and 2.

The skeleton is a larger mass and in the living (*i.e.*, fresh, wet) state may average a sixth of the total body mass; however, the bone minerals account for only about one-fourth of the total skeletal mass and the water, protein and fat components are included in the estimate of the total body content of these substances.

"Fat" in Figures 1 and 2, and as discussed elsewhere in this chapter, is pure fat obtained by ether extraction of the whole body. Adipose tissue is not, as is sometimes supposed, pure fat. From Bozenraad's old studies[5] it is often concluded that human adipose tissue is 80 to 85 per cent of pure fat. Actually, Bozenraad merely reported that when he dried samples of adipose tissue in an oven they lost an average of 15 to 20 per cent of their weight. Bozenraad was well aware of the fact that adipose tissue contains connective tissue, blood vessels and cell walls and he did not suggest that this dried adipose tissue was simply fat. Bozenraad found the water content of the adipose tissue in emaciated persons to be considerably greater than in well-nourished persons. In seven emaciated bodies water averaged 31 per cent of the abdominal "fat," 33 per cent of the heart "fat" and 25 per cent of the kidney "fat." The corresponding averages for 14 well nourished subjects were 12, 18 and 14 per cent, respectively.

Direct Analyses of Bodies.—Figures 1 and 2 are syntheses of a wide variety of data from both direct and indirect analyses of human bodies. Indirect methods, to be considered later, show great promise of practical application but direct analyses are the final reference on which indirect computations must be based.

The technical and legal complications of direct analyses of whole human bodies are such that very few results have been reported in the century since attempts began in this direction. The early work was summarized in the first and subsequent editions of Vierordt's Tabellen[70] but the technical methods then available severely limited the utility of the older data.

In Table 7 are summarized the only reliable modern data on the gross composition of adult human bodies. A total of five bodies have been analyzed, only two of these can be considered representative of normal bodies and one of these, that of the man aged 46, is not free of suspicion of abnormality.

TABLE 7

Direct analyses of entire adult cadavers by Mitchell *et al.*[51] for a man aged thirty five, by Widdowson, McCance and Spray[69] for a woman aged forty two and two men aged twenty five and forty eight, and for a man aged forty six by Forbes, Cooper and Mitchell[23]. The woman committed suicide by drowning. The forty six year old man died a week after a cerebral injury sustained in an accident. The twenty five-year old man died of uremia, the thirty five-year old man died in heart failure with mitral disease and the forty eight year old man died of infective endocarditis in a grossly edematous state. Here 'fat' is ether extract and 'protein' is 6.25 times nitrogen.

				Per Cent of Total Weight				Water as per cent of Fat free Weight
Age	*Sex*	*Height cm*	*Weight kg*	*Water*	*Fat*	*Protein*	*Ash*	
42	F	169	45.1	56.0	23.6	14.4	5.8	73.3
46	M	168.5	53.8	55.1	19.4	18.6	5.4	68.4
35	M	183	70.6	67.9	12.5	14.4	4.8	77.6
25	M	179	71.8	61.8	14.9	16.6	6.4	72.6
48	M		63.8	81.5	1.1	12.8	4.8	82.4

All of the bodies in Table 7 were considered to be relatively thin, yet the fat (ether extract) varied from 1.1 to 23.6 per cent of the gross body weight. Equally significant is the variation, in the fat-free mass, of the water content and of the ratio of ash to protein. Clearly, the concept of a constant composition of the fat-free portion of the body finds no support from the only direct data we have for man. The data from animals are far more numerous but they too show considerable variation between individuals.

Body Fat.—Human body fat, as extracted by ether from adipose tissue removed at surgery from the living body, has an average density at body temperature (37° C.) of 0.9000 grams per cc.[0] Variations in fat density are small between sexes, individuals and locations in the body and this low variability, as well as low absolute value, provides the basis for estimating the proportion of fat in the body from the density of the living person[1,4,38,61]. It should be noted, however, that the thermal coefficient of expansion of fat is relatively high, so allowance for this must be made in dealing with dead bodies. In human fat the mean change in density is 0.00074 per degree C., over the range of 15° to 37° C., so that even in the living body the density will be different in a feverish person as contrasted with the same person in hypothermia.[20] Different animal species differ somewhat in the density and thermal expansion of their body fat and in some species, notably the cow and the lamb, subcutaneous and internal body fats have different densities. All of these facts must be taken into account in applying the densitometric method for the estimation of total fats in various animals.

Densitometry.—The non-fat portion of the body has an average density of something like 1.09 grams per cc. at 37° C. but there are individual

variations, the value is altered by gross changes of hydration, as in edema, and it is also affected by changes in obesity.

As a person grows fatter the bone mineral mass (of high density) tends to remain constant while water, connective tissue, and cells as well as fat tend to increase. This follows from the nature of adipose tissue as well as from the further fact that many of the soft tissues of the body must make at least slight adjustments to the increase in total body size occasioned by the developing obesity. More muscle is required to carry around the added weight, blood vessels have to cover more distance, the area of the skin has to increase.

These are complications but they do not prevent highly useful estimates of total fat in the body from its density, the latter being obtained from estimates of the total mass and volume of the body. An early application of densitometry was made by Kohlrausch[4] who used it to demonstrate changes in the body composition of dogs resulting from alterations in nutritional state and in physical exercise. General interest in the method developed later as a result of the work of Behnke and his colleagues in weighing men under water.[1,3] The development of theory and applications are presented by Keys and Brozek[38] and by Siri.[61]

The measurement of the volume of the living body can be made with considerable accuracy by either of two methods. The Archimedean principle of weighing the body under water provides a sensitive measure of body volume but it requires that an estimate be made of the air in the lungs and respiratory passages at the time of weighing.[38] Measurement of this residual air is not particularly difficult with the nitrogen washout method. In the alternative method, first used by Kohlrausch,[42] the body volume is estimated from the application of the gas laws of Boyle and Gay-Lussac to the body in an air chamber of known capacity. The considerable technical difficulties of the latter method seem to be largely overcome by the use of a foreign gas, such as helium, of which a known amount is injected into the gas chamber; the free space is then estimated from a gas analysis on the dilution principle.[61]

Estimation of Body Fat From Densitometry.—As a first approximation, the body mass may be considered to be a mixture of two components of different densities: a non fat portion of mass N with density n and fat of mass F with density f. The volumes of these two masses are of course N/n, and F/f, respectively, and the density D, of the whole body is

$$(1) \qquad D = \frac{N + F}{(N/n) + (F/f)}$$

If the total mass of the body, *i.e.* the gross body weight, is taken as unity, $N + F = 1$, and the proportional mass of fat in it can be calculated conveniently from equation (1) by transforming to

$$(2) \qquad F = \left(\frac{n}{D} - 1\right) \Big/ \left(\frac{n}{f} - 1\right)$$

Rathbun and Pace[54] assumed that n and f have constant values and provided a numerical solution for equation (2) which has been fairly widely

used However, it is now known that their value for fat density is incorrect for living men and that the value for density of the fat-free body is neither a constant nor is it precisely known for any given situation[38,61]

Most theoretical and practical needs for the estimation of body fat are satisfied with a relative answer We have proposed to do this by making comparisons with a "standard body," the body of a clinically healthy man aged 25 who corresponds exactly in body weight with the United States average for given height as recorded in standard height-weight tables By definition, such a body is neither obese nor emaciated, neither overweight nor underweight From measurements on young men selected to correspond with these height-weight requirements, such a "standard" average body is found to have a density of 1.0629 grams per cc at 37° C[53] Bodies with densities less than this figure are, then, relatively fat and densities above this figure refer to relatively lean bodies

These differences can be expressed quantitatively, in terms of the kind of tissue that the body tends to gain or lose when it is maintained in a state of calorie imbalance for some time From experiments on under- and over-eating to produce body weight changes of the order of 10 to 20 kilograms in otherwise healthy men in a period of 6 months, it appears that such weight changes involve what we have termed "obesity tissue" which tends to have a quite constant density averaging 0.9478 grams per cc at 37° C[37]

If we let G be the proportion of the body made up of such obesity tissue, and D is the observed density of the whole body, we may write, similarly to equation (2),

$$G = \left(\frac{1.0629}{D} - 1\right) \Big/ \left(\frac{1.0629}{0.9478} - 1\right) \quad \text{or} \tag{3}$$

$$G = (8.753/D) - 8.235 \tag{4}$$

Suppose, for example we observe a value of D = 1.050 in man Then we have

$$G = (8.753/1.050) - 8.235 = 0{,}101,$$

and we conclude that 10.1 per cent of the body weight of this man is obesity tissue in excess of that to be found in a body having the composition of our standard young man A negative value for G would mean a deficiency of obesity tissue in comparison with the standard

This obesity tissue is comprised of fat, extracellular fluid and "cells" From measurements in the experiments on men gaining weight from overeating, it appears that about 14 per cent of the weight gain is accounted for by extracellular fluid while the remainder is a mixture of fat and cells having an average density of 9.939 grams per cc The density of the fat is known so it is only necessary to have an estimate of the density of cells in order to calculate the composition of this mixture of fat and cells

Our first estimate was that such obesity tissue was composed of 14 per cent extracellular fluid, 62 per cent fat and 24 per cent cells[37] From more recent experimental evidence we believe a better estimate would be 67 per cent fat and 19 per cent cells These values apply to men who are changing weight over a period of some months In a study of women stabilized at different degrees of fatness, Johnston and Bernstein[33] computed the com-

position of their obesity tissue to average 67 per cent fat and 24 per cent cells so extracellular water would be a somewhat smaller fraction than we observed in our men subjects

Alternatively, the composition of obesity tissue can be expressed in terms of fat, water, proteins and other solids, this latter being a very small item Allowing 20 per cent of cells to be made up of proteins the obesity tissue of our men subjects would be made up of about 67 per cent fat, 6 per cent proteins, less than 1 per cent other solids and about 26 per cent water Incidentally, obesity tissue is not identical with ordinary adipose tissue, as mistakenly assumed by some workers [14]

The composition of obesity tissue indicated above applies to weight changes of the order of less than 15 per cent of the initial body weight occurring over a period of some months in persons initially not grossly obese or greatly emaciated In extremely fat people the obesity tissue may be more nearly pure fat while in the emaciated subject the tissue lost from progressive starvation tends to become less and less fat until finally almost all weight loss is cellular material and water

In the previous edition of this book we suggested that the standard reference body of density 1 0629 contains about 14 per cent fat, a figure accepted as within perhaps 2 per cent of the true value by several later investigators[14,61] But from new experiments on men changing weight in which nitrogen balance as well as density and body density were determined, it appears that the true value may be nearer 16 per cent With this figure we can at least make an approximate estimate of the total fat in the body

As an example consider a man who is not extremely obese who weighs 75 kilograms and has a body density of 1 050 Compared with the reference body he has G = (8 753/1 050) − 8 235 or 10 1 per cent of his body weight in the form of obesity tissue But this obesity tissue is 67 per cent fat so (10 1)(0 67) = 6 77 per cent of his weight or 5 08 kilograms is excess fat We have accounted for (0 101) (75) = 7 58 kilograms of our subject's weight as obesity tissue, leaving 67 42 kilograms which has the same composition as our standard body Note 16 per cent of the latter is fat so this particular man is estimated to have a total of 5 08 + 10 78 = 15 86 kilograms of fat in his body

Body Fat From Body Water Measurement —The total amount of water in the body may be estimated on the dilution principle An injection into the blood is made of a known amount of a substance which penetrates and dissolves in all the water of the body but is not rapidly metabolized After time is allowed for uniform distribution a blood sample is drawn and the concentration of the test substance in the water of the blood is measured Water labelled with isotopic hydrogen deuterium or tritium[61] is suitable as the test substance but possibly antipyrine[6] or urea[16] can be used

Measurement of the total body water is useful for its own sake but it also has the advantage that it may be used to estimate the other components of the body, at least roughly The original crude theory was that water represents a fixed fraction of the mass of the non fat part of the body [14] This is not precisely true even in normally hydrated bodies the best evidence being that water represents a range of something like 69 to 74 per cent of the fat free mass This range may be used to calculate limits for

the proportion of fat in the body when the total body water has been measured

Now the total body weight must be the sum of the total body water, W, plus the total body fat, F, plus S, the total body solids, and if we take the total body weight to be unity, we must have

$$(5) \qquad 1 = W + F + S,$$

where W, F and S are the proportions of the three components in the body In the preceding paragraph it was indicated that we have normal limits of 0 69 (W + S) = W and 0 74 (W + S) = W But from (5) W + S = 1 − F so we have the limiting possibilities

$$(6a) \qquad F = 1 - W/0\,69 \text{ and } \qquad (6b) \qquad F = 1 - W/0\,74$$

The application of equations (6a) and (6b) can be illustrated with the case where a man weighing 80 kg who is found to have a total body water mass of 45 kg, *i e*, W = 0 56 From equation (6a) we have F = 0 189 and from (6b) we have F = 0 243 The conclusion is that the man in question has a body in which from 18 9 to 24 3 per cent of the weight is made up of fat Such a calculation is not permissible, of course, in the presence of edema or dehydration

Body Fat From Body Water and Densitometry —It may be suggested that a more reliable estimate of body composition would be obtained from a combination of body water and density measurements We[53] and others have derived equations for this purpose, that of Siri[61] being as follows

$$(7) \qquad F = (2\,057/D) - 0\,786\,W - 1\,286,$$

where D is the density of the whole body and F and W are the proportions of fat and of water in the body But, as Siri pointed out, this combination really does not eliminate the uncertainty about the fundamental assumptions The estimate of the body fat by equation (7) may have a standard deviation around ±1 7 per cent of the total body weight[61]

Subcutaneous Fat —About half of the total fat in man is in the subcutaneous layer, so measurements of subcutaneous fat may give a good index to the total fat of the body[9 10 16 68] Unfortunately, the subcutaneous fat layer varies from place to place and the distribution is not the same in different individuals or in the same individuals at different ages For example, in young children the layer of subcutaneous fat over the triceps muscle of the arm is relatively thick, even in thin children, while the layer on the belly is much thinner In adults, the proportion is reversed, so data from children[58] do not apply to adults However, sampling several sites, or even a single site in persons of a given age, may allow a fairly good estimate of the total body fatness as estimated from densitometry

Equations for the prediction of total body fat or of body density from a combination of measurements of skinfolds at different sites have been developed[9 10 38 55] These show correlations between the values predicted from skinfolds and those obtained from densitometry with coefficients of $r = 0\,85$ to $r = 0\,87$

The simplest way of estimating the subcutaneous fat is to pinch up the skin, with its attached subcutaneous layer, into a fold The thickness of

this skinfold is mainly made up of subcutaneous fat except in extreme emaciation or on such sites as the back of the hand The double thickness of the true skin is only of the order of a millimeter and this is little changed in obesity or emaciation With experience a fairly good subjective appraisal of calorie nutritional status can be made simply by digital pinching but skinfold calipers, used as recommended by a committee of experts[40] allow novice and expert alike to obtain numerical estimates of acceptable reliability[17 38]

The skinfold should be pinched up to the point where the sides are parallel and the thickness is measured with calipers exerting a pressure of 10 grams per square millimeter (single jaw face area) Prolonged application of the calipers should be avoided because, after the initial deformation of the skinfold under the pressure of the calipers with continued pressure there is a slowly progressive compression, particularly if edema is present Advantage may be taken of this slow deformation to evaluate the presence or amount of edema

Instead of using skinfold calipers, the subcutaneous fat thickness in some parts of the body may be accurately estimated from soft-tissue roentgenograms[27 64]

In a group of 52 middle-aged men the correlations between total body fat (from densitometry) and the thickness of the subcutaneous fat measured on roentgenograms was r = 0 75 and r = 0 76 for two sites on the arms and r = 0 58 for the calf[11] A better correlation might be expected if the sum of fat thicknesses at several sites were used

The topographical distribution of subcutaneous fat tends to be an individual characteristic but changes in fatness induced by dietary alterations seem to be shared proportionally by all regions of the body[16] When an obese person loses fat on a reducing diet, if the fat thickness over the triceps muscle diminishes by 10 per cent, then something like a 10 per cent reduction at other sites may be expected This may be disappointing to reducers who hope to get thinner in some places than in others but it means that simple skinfold measurements are useful for following changes in the total fat of the body

Basal Metabolism and the Body Compartments —The basal metabolism is the result of energetic processes in the active mass of the body fat extra cellular fluid and bone minerals make no direct contribution to this basal metabolism Though adipose tissue is not completely inert metabolically, such energy consumption as it exhibits must be attributed to the cells and not to the plain fat in it Accordingly, it would be more reasonable to express the basal metabolic rate in units of the active tissue mass rather than in terms of the gross mass of the body or even of the popular surface area unit In 1950 we showed that much variation otherwise unexplained, is eliminated when basal metabolism is expressed in units of fat free or, better, active tissue mass[39]

For persons of given sex and age the total basal oxygen consumption is correlated to about the same extent with surface area as with the fat-free body weight[33] The utility of the fat-free body weight as a standard of reference is clear when persons of different sex and age are compared[2 14 50] For both males and females over the age range of perhaps 20 to 60 years a

single value can be used to indicate the "normal" metabolic rate The single value of 4 4 ml of oxygen per minute per kilogram of fat-free body weight can be used instead of the customary tables and graphs based on the artificial concept of surface area as the determinant of the basal metabolism

From the foregoing it is an obvious step to suggest the converse, namely that the fat-free body mass may be estimated simply from the basal metabolism [50] With strictly normal, healthy young adults, this estimation is reasonably good but more general application is questionable because of the susceptibility of the basal oxygen metabolism to hormonal and dietary influences

Since it appears that the basal metabolism normally is strictly proportional to the mass of "active tissue" or "cells" in the body, it follows that the basal metabolism should be closely correlated with any measure which, in turn, is highly correlated with the active cell mass Besides the fat-free body weight, such measures are represented by the total body water and by extracellular fluid mass or volume Without benefit of the considerations outlined above, it has been found that, indeed, basal metabolism is highly correlated with the extracellular fluid volume of the body [13 63]

While the statistical correlations emphasized above are of great utility, it is essential not to lose sight of the underlying physiology From the foregoing discussion it might be supposed that all "cells" or all parts of the "active tissue mass" of the body have equal rates of metabolism per unit of mass This is grossly erroneous, as emphasized by Brozek and Grande [7] In man, the brain and liver, together representing only about 4 per cent of the normal body, account for over 40 per cent of the total resting oxygen consumption while the skeletal muscles, amounting to about 40 per cent of the body weight, contribute barely 25 per cent of the basal metabolism These facts go far towards explaining the otherwise puzzling fact that the basal metabolism early in starvation quickly falls far more than would be predicted from a consideration of the change in total cell mass of the body [28]

Somatotypes —Human bodies differ in type and recognition of gross differences in the body type does not depend on measurements of relative weight or of fatness Sheldon[59] has proposed a scheme of "somatotypes" which is supposed to represent the basic bodily characteristic relatively independent of body fatness and this has been rather widely used However, it is clear that these types are not, in fact, independent of the state of nutrition [38 44] "Endomorphy" and "ectomorphy" appear to be primarily impure expressions of the obesity-emaciation continuum, while the meaning of "mesomorphy" is uncertain The fact that Sheldon's somatotypes are related to body fatness and to total body water does not confer any special value to somatotyping, better estimates of these items are available by other and less esoteric means

The Calorie Equivalent of Weight Change —The most common application of information on body weight and composition is in connection with nutritional control and correction of obesity and emaciation What is the calorie equivalent of a given amount of weight gain or loss? How much body weight change can be expected from subsistence on a given diet? The latter question is too complex for detailed discussion within the presently

available space but the underlying basis of this question is in the first question and deserves attention here.

The most superficial approach is to estimate that, since one kilogram of animal fat has an energy value of about 9100 calories therefore an accumulated nutritional deficit of 9100 calories would be attended by a weight loss of one kilogram. This value, or the value of 9000 calories per kilogram of body weight change, is still quoted from time to time. More commonly Bozenraad's data on adipose tissue[5] are misconstrued and it is concluded that one kilogram of body weight gain or loss should be the equivalent of 8000 calories.[19] But adipose tissue and "obesity tissue," that is the kind of tissue actually gained or lost when the diet is changed, are not identical in calories. Obesity tissue gained or lost in a few months as in our own experiments has a value of about 4000 (0.06) + 9100 (0.67) = 6337 calories per kilogram if it were burned in a calorimeter.

But it by no means follows that a dietary deficit of 6337 calories will produce a weight loss of one kilogram. In the first place, the calorie value of the tissues lost is affected by the intensity of the calorie imbalance and the value changes as calorie imbalance continues. During the first few days on a sharply reduced diet the body tends to lose more water than fat and again after the body has become emaciated further reductions in body weight represent water and protein loss more than fat. In both situations the calorie value of the lost tissue is much lower than 6337 calories per kilogram.

Equally important is the fact that, given time, the body weight tends to reach a steady state and the calorie expenditure tends to balance the calorie intake no matter what the level of the latter may be. When we changed the diet of young men from 3500 to 1500 calories daily the weight loss was rapid at first and decreased exponentially with time until calorie equilibrium was achieved with the body weight being 25 per cent less than it had been.[67]

Dole and his colleagues[13] conducted well controlled experiments on five obese women whose diets were alternated between excess and deficiency at 4 day intervals. The observed weight changes corresponded to averages of 2.16 to 3.61 calories per gram. We have found similar values with men for the first few days of dietary change. Later, however, the calorie value of weight change rises to approximate the value of obesity tissue that is around 6000 calories per kilogram.

Body Composition During Growth.—It has long been known that the concentration of water in the body is very high in the fetus and steadily decreases during growth. During intra-uterine development total body water as a percentage of total body weight decreases from 96 to about 78 at delivery and continues to fall thereafter, with no difference between the sexes during the growing years. Table 8 gives averages for total and for extracellular water.[4]

At least a part of the age trend shown in Table 8 is a result of increasing body fatness. That the relative fatness of the body increases during childhood was indicated from densitometric data reported by Zook[72] and Boyd,[4] though the methods used were unsatisfactory. Macy and Kelly[47] estimated averages of 22, 24 and 26 per cent of the body weight represented by fat from boys aged 4 to 6, 7 to 9 and 10 to 12 years respectively, but their material was small and the calculations were based on many assumptions.

including the arbitrary value of 73.2 per cent for the total water in the fat free body.

The variability between out-patients in regard to body weight response to dietary change is great, partly because of differences in activity habits, partly because the truth about dietary intake is not always easy to discover. Obese people are not always heavy eaters, and this is true of children as well as of adults.[31] Since physical inactivity is so often at fault, we prefer to see reduction in obesity achieved partly by reducing the diet, partly by increasing the exercise. But this certainly affects the calorie equivalent of weight loss.

TABLE 8.—AVERAGE PERCENTAGES OF THE TOTAL BODY WEIGHT REPRESENTED BY TOTAL BODY WATER AND BY EXTRACELLULAR WATER AND THE RATIO OF INTRACELLULAR WATER TO TOTAL BODY SOLIDS DURING INFANCY AND CHILDHOOD. DATA FROM FRIIS-HANSEN.[24]

	0 to 11 Days	*11 Days to ½ Year*	½ to 2 *Years*	2 to 7 *Years*	7 to 16 *Years*
Total Body Water	77.6%	72.2%	59.5%	63.1%	58.4%
Extracellular Water	41.6%	33.7%	26.2%	24.7%	19.9%
Intracellular Water ÷ Total Body Solids	1.61	1.38	0.82	1.04	0.93

Suppose one fat person loses 50 pounds of "obesity tissue" while another combining exercise and reduced food, has a net loss of 50 pounds but has gained 10 pounds of muscle tissue. The former has achieved his weight loss at a cost of about 140,000 calories, the latter has lost 60 pounds of obesity tissue and gained ten pounds of muscle, making a net equivalent of about 168,000 calories. We approve more of the second person's accomplishment.

Optimal Characteristics.—All of the foregoing discussion leads to the conclusion that the specification of "optimal" or "ideal" weights, as well as diets, is a hazardous business. For body weight and relative obesity, at least, the only point on which there will be full agreement is that major departures from the population average should be avoided. There is no doubt that there is an excess mortality penalty in later life associated with marked overweight at the time of application for life insurance. However, the primary data are for major degrees of overweight, from 20 to 75 per cent above the standard average body weight at given height and age, the majority apparently being something like 50 pounds heavier than the average of the population. But to suggest that the major national health obstacle in the United States is obesity because perhaps a tenth of the population may be 10 per cent or more above the average body weight is more than can be sustained from present evidence. Is there actually any serious health hazard necessarily associated with 10 per cent overweight? At what ages? And can we disregard the question of obesity versus overweight? Much more research is needed before scientifically acceptable answers to these questions will be at hand. One thing seems certain. The elimination of gross overweight among Americans c[illegible] by itself, be expected to

bringing our adult mortality experience to a level to compare favorably with that in such countries as the Netherlands and the Scandinavian countries[38] A more penetrating analysis of obesity rather than mere body weight might reveal more scope for improvement

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Chapter 2

The Physiology of the Gastrointestinal Tract and its Bearing on Nutrition

By JESSE L BOLLMAN

THE many studies of the physiology of the gastrointestinal tract have umulated such extensive material that a complete review of the sub- cannot be made Nor would such a review be final and complete in single phase of gastroenterology New techniques cinefluoroscopy, e rapid and exact measurement of pressures within the gastro intestinal , improved chemical knowledge and methods with isotopes hormones nzymes continue to advance our detailed knowledge of gastro-intestinal on Many of these advances open vistas to fields which were pre- y not known to exist There is no area in the gastro-intestinal tract which can be completely described as to activity and function without re sort to some degree of speculative assumption However, our coordinated knowledge of the gastro intestinal tract is such that new knowledge will ring advancement rather than reversal of our present concepts

Nutrition may be compared to modern methods of manufacture In ach instance the crude materials as they occur in nature pass through two stinct processes before emerging as the finished product In the first ocess the natural materials through a series of coordinated steps are nsformed into basic forms suitable for utilization for many purposes is is the role of the processing plants in relation to manufacture and of gastrointestinal tract in relation to nutrition In the second process basic materials either are used directly or are used as building units in the manufacture of the finished product This is the role of manufacturing in the physical world and of nutrition in the biologic world The gastro-intestinal tract is the portal of entry and the site of the initial transformations of the food materials from the forms in which they occur in nature into the basic nutritional elements

Phylogenetically the digestive mechanism has been efficiently adapted to the biologic environment of the species The single celled organism engulfs its food digests it within itself with its own enzymes, and expels the waste residue In the unicellular organism all the processes involved in nutrition necessarily occur in the organism as a unit In the slightly more complex forms of animal life the digestive tract is a simple tube Of this simple digestive mechanism there are many progressively complex variations in various progressively complex organisms or animals In man the digestive processes occur in a tube contained in the body cavity and composed of several highly specialized parts The changes in the digestive mechanisms are adapted to such factors in the biologic environment as the

character of the food, the method of procuring that food, and (especially) the organism's need for time to perform other necessary biologic activities than obtaining and ingesting it. The digestive tract is greatly modified in many species of animals to meet the special requirements involved in the procuring and digesting of their appropriate foods. Some species, however, have ceased to exist when unable to adjust themselves to alterations in quality as well as quantity of food supply. It should be noted here that the following statements about the physiology of the gastro-intestinal tract apply to that tract as found in man.

It is important, first, that the gastro-intestinal tract should be considered as a single organ for by means of its complex and intricate mechanisms for coordination, it is a physiologic unit. Its general functions are (1) to receive in an acceptable form the crude materials ingested, (2) to store the ingested food until it can be digested, (3) to propel the ingesta through the various portions of the tract for mechanical manipulation and chemical alteration so that they may become basic substances which can be absorbed and used in assimilation, (4) to absorb these basic substances and (5) finally to expel what is unusable. In addition, the gastrointestinal tract plays a role in maintaining a constant concentration of many substances in the body by limiting the absorption of certain substances and by providing means of excretion of others.

GENERAL ANATOMIC AND PHYSIOLOGIC FEATURES OF THE DIGESTIVE SYSTEM

Anatomic Features.—*The digestive tract is a muscular, mucosa lined* tube that begins at the lips and ends at the anus. Though sections of this muscular tube have particular anatomic features which have been developed for the performance of special functions, the main anatomic arrangements are similar throughout the length of the tract. Anatomically, the gastro-intestinal tract consists essentially of two reservoirs of which one receives the ingested food and the other the undigestible refuse, connected by a tube designed to afford intimate contact between its content and the circulating fluids of the body.

The portion of the digestive tract that functions as a simple canal, the portion from mouth to stomach is lined with epithelium which is a transition from that of the skin. The lumen of the gastro-intestinal tract is covered by a mucosa composed of simple columar epithelium. The histologic characteristics of the mucosa differ in the various parts of the tract, depending upon the specific functions of each. These differences in the mucosa include differences in thickness, types of glands and constituent cells, form, and fixation to underlying structures. Compared with the mucosa in the rest of the tract, the mucosa in the fundic region of the stomach is relatively thin and loose. The glands of the fundic mucosa are relatively large and contain the two specific types of cells, parietal and zymogen which are considered to produce respectively, hydrochloric acid and pepsin. The outstanding characteristics of the mucosa of the small intestine characteristics limited to it, are circular folds and leaf-like structures, the villi, which

greatly increase the surface area. The glands of the large intestine differ particularly from those of the small intestine in being longer. Though mucus producing cells occur in the mucosa throughout the length of the gastrointestinal tract there is a characteristic group of glands located in the first portion of the duodenum which appear to have the special function of producing mucus.

The propulsive force of the gastrointestinal tract resides in the coats of smooth muscle within its walls. Throughout the tract the muscle is in two coats, an outer longitudinal coat and an inner circular coat, except in the stomach, where the circular coat is mesial and there is an inner oblique coat, and in the large intestine where in some species of animals including man the longitudinal muscle fibers are grouped into bundles. Each section of the gastrointestinal tract having a specialized function is capable of being separated from the following section by means of specially developed rings of muscle, the sphincters. These sphincters not only prevent the ingesta from passing caudally too rapidly for efficient digestion but also prevent the gastrointestinal content from going cephalically.

Other coats in the wall of the gastro-intestinal tract are the muscularis mucosae, a thin layer of smooth muscle just beneath the mucosa, the submucosa, a layer of loose irregularly arranged connective tissue interposed between the mucosa and the circular coat of muscle in the intestine and the oblique coat in the stomach. Almost the entire length of the tract is covered with reflections of the peritoneum.

The blood and lymph vessels of the gastrointestinal tract are generous in number, as its function as portal of entry for foodstuffs would indicate, and in general are similar throughout in arrangement. Their main functions are to furnish an adequate supply of blood to the mucosa and to drain blood and lymph away from it. These vascular channels carry the blood containing the substances absorbed from the intestine and are the anatomic division between the physiologic processes of digestion and assimilation.

The nerve supply to the gastro-intestinal tract consists of an extrinsic and an intrinsic part. These parts are similar in principle throughout the length of the tract. The extrinsic nerves reach the tract by way of the vagal and sympathetic nerve pathways. The intrinsic nerve mechanism is composed of an intricate system of ganglia and plexuses within the walls of the tract. It should be noted (1) that in general the motor and secretory nerve fibers are located in the vagal and the inhibitory fibers in the sympathetic system, although fibers for each of these physiologic activities appear to be in both systems, and (2) that most of the activities of the gastro intistenal tract can be maintained to a certain extent without the action of the extrinsic nerves.

Physiologic Features.—Probably the most outstanding general physiologic characteristic of the digestive tract is the number of mechanisms that have been developed for the coordination of the specialized functions of the different components of the tract and the remarkable manner in which their action is integrated. In relation to the initiation of this series of mechanisms for coordination the special senses—sight, smell and taste—and such sensations as thirst and hunger should not be underemphasized. The subsequent coordination of the digestive mechanisms is normally carried on

The Cardiac Sphincter.—Regurgitation of swallowed food from the stomach into the esophagus does not occur normally because of the absence of an effective force to propel the food orad, the force of gravity, and the position of the stomach. In addition, there is an ill defined and weak sphincteric mechanism, under reflex control, at the entrance of the esophagus into the stomach. This sphincteric mechanism under normal physiologic conditions appears to be of less importance in maintaining the caudal progression of the food than the other factors mentioned.

THE STOMACH AND DIGESTION

The stomach is the great reservoir for food in the first or salivary stage of digestion. In its digestive capacity, it serves three important functions: (1) it receives and stores the swallowed food; (2) it maintains the second or gastric stage in the mechanical and chemical processes of digestion, and (3) it discharges its contents, the chyme, into the duodenum in accordance with the functional capacity of the intestine.

The stomach is divided into three parts—cardia, fundus, and pylorus. The last two are more important physiologically than the first. The fundus, the largest division, not only serves to store food but is also the site where the major portion of the digestive elements of the gastric juice is secreted and the largest part of gastric digestion occurs. By means of its large content of muscle, the pyloric region supplies the mechanism for manipulation and expulsion of the gastric contents.

The Motor Mechanisms of the Stomach.—The stomach, as a reservoir, exhibits a remarkable capacity for adapting its size to the amount of food ingested. The empty stomach is contracted, its walls in apposition except for the region containing air. Meals of different consistencies behave differently in traversing the stomach. Liquids appear to take the path of least resistance and pause in the stomach for only brief periods, if at all. The first aggregates of semisolid food that enter the stomach pass along the greater curvature, where they form a layer over which the next accretions of food accumulate; the last of the meal remains for a short time next to the cardia. This maintenance of the ingesta in layers permits gastric digestion to begin in the outer layers while salivary digestion is continuing in the large mass of food in the body of the stomach. Solid food, immediately after ingestion, forms a ball at the cardiac end of the stomach and then slowly progresses toward the greater curvature and the pylorus.

The motor mechanism of the stomach serves three purposes: (1) by tonic contractions it keeps the gastric mucosa in contact with the varying amounts of gastric contents; (2) by simple movements it manipulates the food on the surface of the mucosa and so mixes the outer layer of ingesta with the gastric secretion, and (3) by means of strong contractions, particularly in the pyloric region, it triturates and mixes the gastric contents mechanically and finally expels them into the duodenum.

The movements of the stomach are complex and not completely understood; the results of many of the observations of gastric motility are not in accord with one another; the whole subject is in rather a confused state. It should be noted, however, that the stomach must be able to perform its

functions under many adverse circumstances It may be forced to accept food of varying quantity and quality at almost any time under almost any condition It would not be surprising if, after being subjected to such unphysiologic treatment, the stomach developed a certain amount of versatility in performing its tasks and did them in more than one way

The tonicity of the musculature in the walls of the stomach maintains the gastric mucosa in intimate contact with the contained food, regardless of the bulk of the latter Hence the gastric secretion is brought into contact with the food immediately upon leaving the lumen of the gastric glands Both musculature and movement in the fundic region of the stomach are relatively weak and do little more than maintain pressure upon the gastric contents and mix them with the gastric secretion Musculature and movement in the pyloric region of the stomach, however, are both powerful and not only break up food masses and aggregates but also sweep them toward the duodenum

The food is propelled through the stomach by waves of peristalsis This type of movement will be described in connection with the movements of the intestine, for it has been easier to study peristalsis in the intestine than in the stomach The majority of the gastric waves of peristalsis appear to begin as faint ripples in the cardia or fundus shortly after the food mass has reached the pylorus and to become more powerful as they pass into the region of the thick musculature of the pylorus It is an undecided question whether all the gastric peristaltic waves pass over the entire length of the stomach to the duodenum The evidence would indicate that at least a majority of them do reach the duodenum and are the most important force in gastric evacuation Occasionally, strong, deep waves of peristalsis followed by more or less complete relaxation traverse the stomach and exhibit, in general, a pulsating type of movement This type of movement performs a function not greatly dissimilar to the segmentation movements of the intestine, to be described later

The Emptying of the Stomach —The mechanisms responsible for the rate at which the stomach is emptied must be coordinated to permit the maximal amount of gastric digestion to occur, including mechanical and chemical alteration of the food for intestinal digestion, and to achieve evacuation of the gastric contents, the chyme, into the duodenum in amounts which can be efficiently digested in the intestine It is obvious that several important mechanisms, involving both motility and secretion, must be coordinated in order to accomplish these physiologic objectives in an orderly manner It has required a great deal of research to explain these mechanisms, unfortunately, their complete story cannot even yet be told

The rate of gastric evacuation increases progressively from early digestion until the process is completed and depends not only upon the presence of peristalsis of adequate depth but also, to a considerable extent, upon the consistency, amount and kind of ingested food Liquid and semisolid foods which require very little gastric digestion and are acceptable for digestion in the intestine, pass through the stomach very quickly The onward rush of liquids is, in all probability, due to some extent to the force of gravity Gravity may also be a factor in the evacuation of food which has been suitably prepared by gastric digestion The tonus of the musculature of the

gastric walls, which keeps the gastric mucosa in contact with the ingesta and the cavity of the stomach approximately equal to the bulk of gastric contents, may also aid in gastric evacuation Since with the exception of the force of gravity, however, there are more factors to cause resistance to the propulsion of the food caudally than orally regurgitation would occur if intragastric pressure were an important factor in gastric emptying The amount of food ingested affects gastric emptying A large meal requires a longer time to leave the stomach than a small meal, but the rate at which the former is evacuated is the more rapid The type of food affects the rate of gastric evacuation Proteins are evacuated more slowly than carbohydrates, fats more slowly than proteins Though there is some evidence to show that when absorbed from the intestine digestion products of all types of food depress gastric motility, so far as fats are concerned there is a specific mechanism involved Fatty chyme upon entering the intestine releases a chalone, enterogastrone, which depresses gastric tone and motility Gastric emptying time with a standard meal is quite constant for a specific individual and varies little from day to day though considerable individual variation exists

The Mechanism of the Pylorus —The musculature of the pyloric region of the stomach is thick and strong and the exit of the stomach is guarded by a well defined ring of muscle, the pyloric sphincter Considerable controversy has ensued as to the importance of the pyloric sphincter in the evacuation of the stomach and the mechanism that controls its action It would appear that the beautiful hypothesis of acid control of the sphincter must, at least in part be abandoned that the sphincter itself is normally not essential for either the retention of gastric contents or the orderly passing of chyme into the duodenum but plays an almost passive part in gastric evacuation The sphincter is probably of as great importance in preventing duodenal regurgitation as in resisting gastric evacuation Acid in the stomach does not appear to exercise specific control over the pyloric sphincter or the pyloric musculature On the other hand acid in the duodenum appears to inhibit the entire pyloric mechanism and so retard the progress of the chyme Normally the sphincter is quiescent and relaxed it is strongly contracted only when a gastric wave reaches it The active sphincter exhibits cyclic activity, and opening of the sphincter is a characteristic phase of the cycle, but the sphincter is relaxed during more than half of each cycle It would appear that the control of gastric evacuation depends mainly upon the pylorus as a whole and the first part of the duodenum and that the mechanisms involved are both nervous and humoral

The Secretory Mechanisms of the Stomach —The gastric mucosa is divided histologically into three parts—the cardiac, the fundic and the pyloric The line of demarcation between the fundic and the pyloric regions is much more definite than that between the fundic and the cardiac regions From the physiologic viewpoint it is sufficient to state that almost all the acid and almost all the enzymes of the gastric secretion are formed by the glands of the fundic mucosa and that the pyloric mucosa produces only a scantp secretion neutral or slightly alkaline in reaction

Gastric seccretion normallo occurs in three definite waves The first wave begins with the thought of food or the recognition of the presence of

food in association with the sensation of appetite, the second begins with the entrance of food into the stomach, the third follows a latent period after the evacuation of the chyme into the intestine. These three progressive waves of secretion depend upon the different types of stimulation which bring about activity of the gastric glands; the time at which they occur has a definite relation to the gastric cycle initiated by the presence of the meal and the consumption of that meal. These three waves are called the cephalic, the gastric, and the intestinal phases of gastric secretion. They are due to both nervous and humoral mechanisms.

Cephalic Phase of Gastric Secretions.—The cephalic phase of gastric secretion is so called because the stimulus that causes it is a nervous one. The environmental factors associated with eating, thinking about, seeing, smelling, and tasting food, cause an initial secretion of gastric juice. This is the result of a nervous reflex. The appetite juice is usually not great in amount, but has a high concentration of pepsin. This initial secretion of the gastric mucosa is very important, for the succeeding mechanisms for stimulating the gastric glands and, to a lesser extent, determining the rate of gastric evacuation depend upon its action.

Gastric Phase of Gastric Secretion.—The gastric phase of gastric secretion is due to direct stimulation of the gastric mucosa by the ingested food. The mode of stimulation is both mechanical and chemical. The mechanical stimulation is caused by the distention of the walls of the stomach by the food. The amount of gastric secretion produced by this mode of stimulation is probably not great. The gastric glands are also stimulated by chemical substances present in the food or produced by gastric digestion. It is possible that some food substances stimulate the gastric glands directly. There also exists a humoral mechanism for gastric secretion, but it has not been conclusively proved that the exciting agent is a hormone.

The Intestinal Phase of Gastric Secretion.—A short time after the chyme has passed into the intestine, the rate of gastric secretion is either increased or decreased, depending upon the kind of food that has been ingested. Gastric secretion is increased following the eating of a mixed meal or one predominantly protein. On the other hand, gastric secretion is decreased after the ingestion of a meal predominantly fat or (though to a lesser degree) carbohydrate. The increase in gastric secretion is due to a humoral stimulation of the gastric glands. The exciting agents are probably secretogogues. A considerable portion of these secretogogues are removed from the portal blood by the liver. Conditions which allow blood from the intestines to bypass the liver increase this phase of gastric secretion. The cause of the decrease in gastric secretion in the presence of fat in the intestine is due to the release of the chalone, enterogastrone, which has been mentioned previously in connection with gastric motility.

The Control of Gastric Acidity.—There has been a very great deal both of research and of speculation with regard to the problems of (1) the formation of the hydrochloric acid of the gastric secretion, (2) primary acidity, and (3) the regulation of acidity. The first two problems do not appear to differ fundamentally from the problems concerned with the elaboration of other glandular products, except for the unique fact that a mineral acid is involved. The regulation of gastric acidity, however, seems to depend upon many

factors among them the following (1) amount and kind of ingested food (2) changes in the rate of gastric secretion, (3) secretion of mucus, and (4) regurgitation from the duodenum The significance of the last two though, has probably been overemphasized

THE SMALL INTESTINE AND DIGESTION

The small intestine is the site in which the most important of the digestive processes occur and from which the bulk of the end products of digestion are absorbed and leave for the other tissues of the body It also receives the secretions of the largest accessory glands of digestion the pancreas and the liver as well as the secretion of its own mucosa Though the organism can be maintained without other parts of the gastro-intestinal tract a certain minimal amount of small intestine is essential for life

The small intestine is divided into three parts—duodenum jejunum, and ileum The anatomic and physiologic differences among these three parts are not great Anatomically, the thickness of both the musculature and the mucosa progressively decreases caudally physiologically, the amount of activity particularly with regard to motility also decreases and in a similar manner

Movements of the Small Intestine—It is questionable whether the small intestine is at any time completely inactive throughout its entire length, though depending upon the ingestion of food, the amount of activity varies greatly After a fast of twenty four hours or longer the ileum is usually quiescent, but there is usually some activity though it is very feeble in the duodenum and the jejunum Immediately after the ingestion of food a regular cycle of activity occurs There is a rapid motor response followed by prolonged activity which includes all types of intestinal movements and persists throughout the digestive cycle The increased activity following the taking of food passes as a wave from the duodenum to the terminal portion of the ileum Its passage in a normal manner depends upon the continuity of the intestine Liquid foods cause less response than solid foods There is a gradient in the amount of activity, which decreases progressively from the duodenum to the terminal portion of the ileum

The movements of the small intestine serve four functions (1) they propel the food caudally through the lumen at a rate consistent with efficient digestion and absorption (2) they mix the ingesta with the digestive secretion (3) they maintain the mucosa in intimate contact with the intestinal contents for absorption, and (4) they improve the flow of blood and lymph particularly the latter in the blood and lymph vessels of the intestinal walls

The intestinal contents are propelled caudally by waves of peristalsis The classic description of a peristaltic wave is that it is a wave whose progress is marked by localized relaxation or inhibition followed by localized contraction which decreases the intestinal lumen The wave of relaxation may be more apparent than real Peristaltic waves are of two types slowly moving contractions which proceed for relatively short distances and swift movements the peristaltic rushes which sweep without pause for long lengths of the intestine and push the intestinal contents caudally—or

too much pressure is developed, cephalically—through the incompletely closed lumen

The mixing of the ingesta within the intestine, as well as the keeping of the mucosa in direct contact with the intestinal contents and the expelling of the blood and lymph from the walls of the intestine, is accomplished by segmentation contractions Contractions of this sort isolate short lengths of the intestine and mix the contents in much the same manner as, if it were possible, alternately squeezing two neighboring lengths of intestine by hand would do These segmentation movements are of two types—the regular and the irregular The first are rhythmic contractions that appear as muscular beats They appear to occur much less frequently than the irregular type and are normally observed most often in the fasting state The rate of rhythmic contraction is constant for any given loop of intestine and, as previously mentioned, decreases with increase in distance from the pylorus The irregular segmentation movements are similar to the rhythmic ones, but they are not constant in either rate or amplitude

There are other less constant and less definite types of intestinal movements Changes in the tone of the muscles in the intestinal wall produce more or less stationary waves, which may or may not have segmentation contractions superimposed upon them Pendular movements causing the contents of short loops of the intestine to pass back and forth are apparently brought about by the simultaneous contraction of large masses of the muscles in short lengths of the intestine The mechanisms of such movements are not well understood Peristalsis that progresses in the oral direction is known as antiperistalsis There appears to be no question that antiperistalsis does occur, but this type of movement is very difficult to observe under normal physiologic conditions Normal occurrence of antiperistalsis has been observed most commonly in the duodenum and the colon, but under experimental conditions it can be induced anywhere in the intestinal tract

The Digestive Secretions in the Small Intestine —The digestive secretions in the small intestine come from three sources—the pancreas, the liver, and the intestinal mucosa The pancreatic secretion contains three major enzymes—trypsin, amylopsin, and steapsin These are respectively, proteolytic, hydrolytic to carbohydrate, and hydrolytic to fat The important digestive constituents of the bile are the bile salts, which aid in the emulsification of fats The secretion of the intestine contains many enzymes whose action completes the digestion of several substances One constituent of the intestinal secretion, *enterokinase*, is unique in that it activates the proteolytic enzyme, trypsin

Mechanism of Secretion by the Pancreas —Pancreatic secretion has both a nervous and a hormonal control It appears that, owing to a nerve reflex, the sensations associated with the taking of food cause a secretion by the pancreas The amount of this pancreatic secretion is difficult to determine, but it is probably not great The presence of hydrochloric acid, fats, fatty acids, and some other food products transforms or releases from the intestinal mucosa a hormone, secretin, which stimulates the pancreas to secrete This hormonal mechanism is responsible for the secretion of most of the pancreatic juice

Mechanism of the Secretion and Discharge of Bile —Bile is secreted continuously by the hepatic cells but the rate varies with many factors These factors are not very well understood During interdigestive periods, however, the bile secreted is stored in the gallbladder in species of animals in which such a viscus exists The bile is made to enter the gallbladder by the action of a sphincter at the end of the common bile duct in the duodenal wall The capacity of the gallbladder to store bile is greatly enhanced by its mucosal absorption of the water content of bile Both nerve and hormonal mechanisms cause the gallbladder to empty though the nervous mechanism is difficult to elicit The presence of certain foods in the intestine causes the gallbladder to empty and the intestinal mucosa contains a hormone cholecystokinin which specifically causes the gallbladder to contract and evacuate

Mechanism of Secretion by the Intestine —Knowledge of the mechanism of secretion by the intestine is incomplete It would appear that both a nervous mechanism and a hormonal mechanism exist to control the secretion of the intestinal juice, succus entericus Mechanical stimulation of the intestinal mucosa causes an immediate secretion of intestinal juice with a high content of mucus A hormonal mechanism for the secretion of succus entericus appears to have been demonstrated The hormone, enterocrinin, is found in the intestinal mucosa and appears to stimulate the intestinal gland cells directly

The Ileocolic Sphincter —The rapid passage of intestinal contents from the ileum to the colon and the reflux of colonic contents into the ileum are partially prevented by a sphincteric mechanism at the junction of ileum and colon, the ileocolic sphincter This sphincteral mechanism is rather weak and not well defined Similar to that of both the small and the large intestine its action can be affected by the extrinsic nerves but is, on the whole autonomous In some species of animals intestinal contents particularly fluids pass readily back and forth through this sphincter

THE LARGE INTESTINE AND DIGESTION

The large intestine is the terminal reservoir of the gastro-intestinal tract It performs several important functions It is the site where the essences of the last dregs of digestion are filtered into the circulation and certain substances are withdrawn from the blood and excreted And since the digestive processes require a fluid medium it is adapted for rapid absorption of fluid whose function is to afford such a medium It also serves as an incubator to permit bacteria to reduce materials resistant to the previous processes of digestion Finally, after everything that the body can use has been absorbed and the residue decreased and dehydrated it indicates by means of a sensory mechanism the futility of longer retention of unprofitable material and expels it from the body This last process is a curious mixture of the voluntary and involuntary its physiologic counterpart is swallowing

The terminal reservoir of the gastrointestinal tract consists of the cecum the colon and the rectum The colon has ascending transverse and descending portions These are as physiologic as they are anatomic but be-

cause of limitation of space it is necessary to consider their functions together

Movements of the Large Intestine —As with the stomach, the results of the different studies of the movements of the large intestine are rather confusing This confusion, chiefly due to differences in results of observations, is due in part to the fact that there is great variability in the activity of the large intestine in different species of animals In general, however, it may be stated (1) that the large intestine is usually quiescent, (2) that it is usually inactive while the contents of the ileum are being evacuated into it, and (3) that, though propulsive movements predominate in it, they frequently occur without effect in moving the contents caudally To a certain extent, the contents of the large intestine are made to progress caudally by the pressure exerted as a result of the filling of the proximal portion of the colon with the material expelled from the ileum The gradual physical alteration dehydration, that occurs in the contents of the colon favors their progression A gradient of activity is also found in the colon The cecum is more active than the other portions of the large intestine The movements of the colon are relatively sluggish compared with those of the small intestine, only the movements of the terminal portion are powerful These findings are in accordance with its function as a reservoir and mechanism for expelling the fecal material Though peristalsis has been observed throughout the length of the large intestine the waves are difficult to detect and are relatively weak and slow The special bundles of longitudinal fibers found in the colon can contract and form sacculations Waves of antiperistalsis have also been observed in the proximal portion of the large intestine but like the peristaltic waves, are difficult to detect The obvious function of such movements would be to retard the passage of the material received from the ileum and thus afford opportunity for more rapid and complete absorption Tonic contractions occur in the colon both with and without superimposed smaller contractions An increase in activity of the large intestine occurs after the ingestion of food if, at the same time, there is an adequate bulk of colonic contents

The evacuation of the undigestible residue is under nervous control and consists of a complex reflex act which may be aided or inhibited by the contraction of certain voluntary muscles The length of large intestine involved in the act depends to a great extent upon the species of animal and the type of food ingested The musculature of the intestine is insufficient to expel the residue in species in which considerable dehydration occurs The act is initiated by a sensory mechanism stimulated by the entrance of fecal material into the rectum The evacuation begins with an inhibition in the tone of both the anal sphincters associated with contraction of the musculature of the rectum and a variable length of the colon If the resulting pressure is not sufficient to expel the residue the glottis closes and the abdominal muscles contract, increasing intra-abdominal pressure and aiding the evacuation

CHEMICAL PROCESSES OF DIGESTION

The chemical processes of digestion break down the complex organic molecules of ingested foodstuffs into simpler, smaller, more soluble, and

more diffusible molecules and so reduce food to molecules that are at once readily absorbable and readily available, as building blocks for the synthesis of protein and fat characteristic of the individual rather than of the source of the food. Chemical processes essentially the same as in the digestion of protein and fat occur in all body tissue in autolysis and in the continuous metabolic breakdown of protein and fat for energy-producing reactions and for repair.

Hydrolysis.—The splitting of complex protein, carbohydrate, and fat molecules into simpler compounds occurs to some degree, usually a very slight one, when they are exposed to water. The rate of hydrolysis and the amount of material hydrolyzed may be greatly increased by heat and still more greatly increased by the addition of acid or alkali but some of the products of hydrolysis are destroyed by this treatment. Biologic digestion is the same chemical hydrolysis accomplished rapidly at body temperature with the aid of specific enzymes. The essential process is the addition of one molecule of water to the original compound at a definite linkage with simultaneous division of the compound into two fractions, one of which then contains the hydroxyl group of the added water and the other the hydrogen radical. The process is fundamentally similar for all proteins, fats, and carbohydrates.

1. Protein: $R\,CH_2\,NH{-}CO\,R + H_2O \rightarrow R\,CH_2NH + HOOCR$
2. Fat: $C_3H_5\,(OOCC_{15}H_{31})_3 + 3H_2O \rightarrow 3(C_{15}H_{31}COOH) + C_3H_5(OH)_3$
3. Carbohydrate: $C_{12}H_{22}O_{11} + H_2O \rightarrow 2(C_6H_{12}O_6)$

In each of the above reactions, the action is inhibited by the accumulation of the end products. The rapid removal of the end products by absorption from the intestine permits these hydrolyses to continue rapidly to complete disposal of the substrates involved.

The Digestive Enzymes.—All the enzymes of the gastro-intestinal tract have some degree of specificity, proteolytic enzymes acting only on protein, lipolytic enzymes only on fat, and amylolytic enzymes only on carbohydrates. Many absolutely specific enzymes have been purified and isolated, as for example, maltase, which hydrolyzes maltose to two molecules of glucose but has no action on sucrose, galactose or other sugars. Many of the proteolytic enzymes are also very specific in their action, hydrolyzing only certain linkages of specific amino acid combinations. Pancreatic trypsin will hydrolyze alanylglycine but not glycylalanine, which contains the same amino acids linked in a different way. A peptide of five glycine molecules is hydrolyzed, but a peptide of three glycine molecules is not. Apparently the configurations of specific enzymes are such that they cannot combine with molecules other than those having contours which they will fit exactly, rather as a key fits a lock. Some enzymes may be master keys and fit more than one type of combination, but others fit only one specific combination. There is growing evidence that the digestive juices contain mixtures of many enzymes, each specific for a specific substance or partially digested product.

The Acid-base Balance in Digestion.—The various digestive enzymes of the gastro-intestinal tract require different degrees of acidity or alkalinity for optimal activity. Some are inactivated and others completely destroyed

by exposure to different acid conditions found in the gastro-intestinal tract The present writer once studied dogs that had permanent fistulas at different levels of the gastro-intestinal tract, samples of the intestinal contents could be withdrawn as desired The gastric juices of the fasting animals were usually strongly acid, pH 1 5 to 2 0, but at times were almost neutral, which suggests that the truly resting stomach is neutral in reaction, but that gastric secretion is easily stimulated The contents of the fasting duodenum, ileum, and colon were usually found to be alkaline, pH 7 0 to 8 0, though the contents of the duodenum were frequently acid when highly acid values were found in the stomach Following a meal, the acidity of the contents of the gastrointestinal tract depends largely on the development of acid in the stomach With each rush of acid chyme from the stomach, short periods of high acidity are common in the duodenum less and less common in the small intestine as the distance from the pylorus becomes greater The rushes of acid chyme are neutralized as they proceed further down the intestine during the course of a rush and are also rapidly neutralized *in situ* by the secretions of the intestine, the pancreatic juice, and the bile The usual reaction in the small intestine after a meal is close to neutrality, pH 6 5 to 7 5 The contents of the colon are usually slightly alkaline but may be slightly acid, especially following a meal rich in carbohydrate Dietary measures may greatly alter the acidity of the contents of the gastro-intestinal tract

Products of Enzymatic Action —Digestion is a continuous process it continues from the time of taking food until the food residue is expelled from the colon Under normal circumstances, it is a very efficient process, one which transforms almost all the available material of the food into readily absorbable and utilizable simple forms Carbohydrates are converted into glucose proteins into amino acids, and fats into fatty acids and glycerol Most plants contain additional substances, which are capable of producing energy when oxidized but which are not utilized by the body these are excreted in the feces unchanged by the process of digestion Cellulose, hemicelluloses, inulin, and pectin are examples of carbohydrates not digested by the digestive juices Bacterial action in the intestine, however, does destroy some of these substances, in herbivorous animals as much as 25 per cent of such substances may be hydrolyzed by bacterial fermentation and absorbed as simple sugars But less than 5 per cent of these substances may be utilized by dogs, the amount utilized by man is even smaller They are therefore of no importance in the diet of a normal person Excessive amounts of cellulose taken as food substitutes greatly increase the bulk of the feces and cause the loss of more food value in this way than would be lost from the same amount of food taken without the filler

The efficiency of digestion is dependent upon the orderly exposure of the food to the action of enzymes Starch is partially digested by the salivary amylase or ptyalin This is accomplished by the hydrolysis of one or more molecules of maltose from the starch molecule at a time, so that a succession of products is formed—soluble starch, erythrodextrin, α-achroodextrin, β-achroodextrin and maltose Salivary amylase is inactivated by free hydrochloric acid in the stomach, but there is an appreciable digestion of starch during the period of mastication and swallowing Swallowed food is

not immediately mixed in its entirety with free hydrochloric acid, depending on the size and character of the meal some salivary digestion continues in the stomach With meals containing bread and potatoes, as much as 75 per cent of the starch may be converted into maltose by salivary amylase within from fifteen to thirty minutes There may be some slight hydrolysis of starch products by the hydrochloric acid of the stomach but there are no amylolytic enzymes in the stomach As soon as the acid chyme is neutralized in the intestine, it is exposed to the action of pancreatic amylase, which is similar to that of the saliva Purified preparations of pancreatic amylase have been made which will digest more than 20 000 times their weight in starch in thirty minutes Maltase which converts maltose into glucose is also present in pancreatic juice along with sucrase and lactase And since the secretions of the duodenum the jejunum, and the ileum also contain amylase, maltase sucrase, and lactase only a small amount of starch or its partially digested products reaches the large intestine When conditions are abnormal or the dietary intake of starch or sugars has been excessive, bacterial action on these residues may produce substances irritating to the intestine as well as excessive amounts of gas

Protein is converted into acid metaprotein by the action of gastric acid on food proteins In the time that food normally remains in the stomach, pepsin digests acid metaproteins and unmodified proteins and converts them into proteoses and peptones No amino acids appear to be liberated Since pepsin acts by splitting peptide linkages, it is apparent that its action is limited to peptide linkages having some special characteristics As soon as the acid chyme is neutralized in the intestine, protein digestion continues, with the aid of the pancreatic juice From this juice three proteolytic enzymes have been definitely isolated Trypsin and chymotrypsin act on native proteins proteoses and peptones which are further broken down into polypeptides These two enzymes have many common properties, but some differences suggest that they hydrolyze only certain specific linkages of the peptide type Carboxypolypeptidase found in pancreatic juice, acts on polypeptides, breaking them down to simpler polypeptides and amino acids This enzyme acts only through the carboxyl group of polypeptides Amino polypeptidase found in the intestinal secretions, hydrolyzes polypeptides into amino acids by acting through the amino group The intestine also secretes a dipeptidase, which splits dipeptides and liberates amino acids

The gastric secretion contains lipase, which splits fat into fatty acids and glycerol Its action is inhibited by the acid of the gastric juice but it is more or less active when the gastric juice is of low acidity It appears to be most active against highly emulsified fats, but the digestion of fat in the stomach is of slight importance compared with the digestion of fat in the intestine The intestinal juices also contain a weakly active lipase Most of the digestion of fat is accomplished by the lipase of pancreatic juice

The phosphatase of the intestinal secretion acts on several groups of such phosphates as nucleotides, glycerophosphates and hexosephosphate This phosphatase is similar to that found in many other tissues of the body It liberates inorganic phosphate and the organic component of the molecule as nucleosides, glycerol or hexose

The digestion and absorption of foodstuffs is a remarkably efficient process Coffey, Mann and Bollman found that the fecal excretion of carbohydrate, protein, and fat constituted only a small percentage of the amount of these substances in the diet of normal dogs When cracker meal was fed, for example, in amounts of from 10 to 150 gm in combination with varying amounts of other foodstuffs, only from 0 3 to 1 5 gm of carbohydrate was recovered in the feces The nitrogen content of the feces was low, too, varying from 0 3 to 0 8 gm And it was more influenced by the bulk of fecal residue than by the protein content of the diet When meat was fed, the amount of nitrogen in the feces was less than 5 per cent of the nitrogen content of the dietary protein, since the fecal nitrogen is largely that of bacterial residue and metabolic products, it was obvious that almost all the dietary protein had been absorbed When lard was fed in amounts of from 10 to 150 gm , the feces contained as little as from 0 5 to 6 0 gm of fat More than 95 per cent of the fat was absorbed regardless of the amount of fat in the diet

Similar results are obtained from the study of normal human beings Only negligible quantities of carbohydrate are found in the feces even when the intake of carbohydrate is great Fecal nitrogen usually amounts only to 1 or 2 gm per day and rarely if ever exceeds 3 gm unless the diet contains an excess of indigestible material (roughage) The quantity of nitrogen in the feces is practically uninfluenced by large variations in the amount of dietary protein Although the quantity of fat in the feces is to a considerable extent influenced by the amount and type of fat in the diet, fecal losses average less than 5 per cent and seldom exceed 7 per cent of the intake when an ordinary mixed diet is eaten, regardless of the quantity of fat in the diet

Absorption from the Stomach —Absorption from the stomach is so slight that it is of little importance from the nutritional point of view When water is given alone, it passes through the stomach and is absorbed from the intestine Alcohol, however, is absorbed to a considerable extent while in the stomach Small amounts of sugars may be absorbed from the stomach but practically no digestive products of protein or fat are absorbed until the food reaches the intestine

Absorption from the Small Intestine —Since in the process of digestion proteins, carbohydrates, and fats are broken down into simple substances, the processes of absorption deal with amino acids, monosaccharides, fatty acids, and glycerol These substances and inorganic salts may be absorbed from the intestine by physical diffusion Absorption is essentially a passage of substances, soluble in water or lipoids, through a complicated colloidal membrane the permeability of which can be altered by intrinsic factors All of the physical forces which influence the passage of fluid through dead membranes are operative in intestinal absorption and these are only modified by the living properties of the intestinal mucosa The influence of the intestinal mucosa may be shown in experiments with perfused rabbit intestine When a 13 5 per cent solution of glucose is perfused through the lumen of the intestine, the passage of sugar to the outer fluid surrounding the intestine is constant for a period of about three hours At this time the

active movements of the intestine cease and the glucose passes very much more rapidly through the dead and dying membrane.

If the intestinal mucosa functioned solely as a "dead" membrane, the rate and direction of transfer of solutes would depend upon the physical factors involved. The chief physical factors concerned in absorption are the permeability of the membrane, the temperature, the diffusibility of the solute, the concentration of solute on both sides of the membrane, surface tension and electrical potential on both sides of the membrane. Each of these factors has been investigated and it has been found that in many circumstances absorption from the gut does not proceed purely according to the known physical laws. The phenomenon of absorption is partly due to certain special properties of living epithelial cells.

Although absorption consists essentially in the passage of materials from the intestinal lumen into the circulatory system across the intestinal mucous membrane, there is also a simultaneous movement of water, electrolytes, lipids and other substances in the opposite direction, that is from blood stream to intestinal lumen. The volume of this exchange is very large. The blood flow to the intestine of an adult is about one liter per minute and isotope studies have shown that about one fourth of this volume passes from the blood vessels as plasma filtrate which is reabsorbed into the portal vein and lymphatics. Studies of the dilution and absorption of isotopic water from the intestine indicate that something near 5 liters of water pass in and out of the gastrointestinal lumen each hour. This volume of fluid must aid considerably in the solution and removal of products of digestion. Absorption of solutes from hypertonic solutions can occur, but such solutions soon become isotonic not only because of absorption of solute but also because for a time more water enters the intestinal lumen than leaves it. Under physiologic conditions strongly hypertonic solutions do not gain entrance into the intestine since they are diluted in the stomach or are released intermittently from that organ in such small amounts as to be quickly diluted in the small intestine.

Carbohydrates pass into the blood from the intestine as simple sugars, monosaccharides. The rate of the absorption of glucose from the intestine increases with the concentration of glucose within the lumen up to the hypertonic concentration of 13.5 per cent. Further increases in concentration as the result, for example, of administered solutions of glucose do not further increase the rate of absorption. The maximal rate of the absorption of various sugars has been found by investigators to depend upon the specificity of the intestine rather than the physical properties of the sugar solution. For rats after a fast of forty eight hours the maximal rate of the absorption of sugar (in grams of sugar per 100 gm. of rat) has been found to be as follows: galactose 0.196 gm., glucose 0.178 gm., fructose 0.077 gm., mannose 0.034 gm., xylose 0.0289 gm. and arabinose 0.016 gm. Absorption of these sugars from the peritoneal cavity shows no such specificity and seems to be entirely dependent upon the physical factors involved. There is some evidence that the absorption of some substances is influenced by the presence of others in the intestine. When in experiment, mixtures of glucose and galactose were fed together, the total amount of sugar absorbed was found to be less than when either was fed alone, and it was found that

glucose disappeared more rapidly than galactose, the reverse of what obtains when the sugars are fed separately One explanation offered of the specificity of the absorption of sugars by the gastrointestinal tract is that the mucosal cells phosphorylate sugars as they are absorbed and the rate of phosphorylation determines the rate of absorption

Protein is absorbed in the form of individual amino acids, an appreciable increase in the amino acid content of the plasma and erythrocytes may be noted after a meal containing protein It has also been shown that the rate of absorption of amino acids reaches a constant level and remains at that level as long as amino acids are present in the intestine Not all substances, however, are absorbed at a constant rate from the intestine Lactates, for example, have been found to be absorbed at rates directly proportional to the amounts fed There is also some evidence to show that the intestinal mucosa may chemically alter amino acids as they are absorbed, but the evidence is not conclusive Larger aggregates of amino acids and incompletely decomposed proteins may sometimes be absorbed, but probably only under special circumstances Sensitization to specific proteins and the allergic reaction to specific proteins given by mouth can occur only in this way, as the digestion products of such proteins are inactive

The course of absorption of fat may be studied microscopically in sections of intestines taken at different times after the ingestion of fat By staining methods fat can be seen accumulating in the epithelial cells as absorption proceeds It occurs in fine particles that gradually become larger and larger until droplets may be formed near the base of the cells The cells may be completely filled with fat except for the cellular border, which apparently does not contain demonstrable fat at any time This free border appears to be composed of lipoid material in which fat is soluble but does not stain while in true solution The lipoid character of the free border of the intestinal mucosa is demonstrated by the fact that lipid-soluble dyes pass through it into the cells, whereas water-soluble dyes pass between the cells Fats are absorbed from the intestine in a hydrolyzed form and pass into the lymph of the intestine for the most part as neutral fat, although a certain portion of the fatty acids are found in the phospholipid and cholesterol-ester fractions Whether complete hydrolysis in the lumen of the bowel is essential for the absorption of fat has not been determined, but evidence indicates that extensive hydrolysis and resynthesis have occurred by the time fat has reached the intestinal lymphatic vessels Bile in the intestine facilitates the emulsion of fat and fatty acids, and pancreatic juice increases the hydrolysis of fat The absence of one or both of these substances greatly impairs but does not entirely prevent the absorption of fat

Analysis of lipids in the intestinal lymph of rats fed tagged fatty acids, both in the free state and as neutral fat, has shown that the lymphatic vessels are probably the only route by which absorbed fats enter the circulation That the lymphatic system is the sole route by which some fat-soluble materials leave the intestine after absorption can be demonstrated in the case of vitamin K A pronounced deficiency of prothrombin rapidly develops in animals deprived of intestinal lymph while taking a normal diet,

this deficiency can be readily and completely corrected by parenteral administration of minute doses of vitamin K Apparently not even small amounts of this vitamin are transported from the intestine by routes other than the lymphatics Other lipid soluble vitamins also appear to be absorbed either with fat or by a similar process, and the lack of absorption of lipid-soluble vitamins becomes a problem when conditions interfere with the absorption of fat

There is great specificity for the absorption of sterols Ergosterol is absorbed but slightly, whereas irradiated ergosterol is completely absorbed The selective nature of absorption applies to other substances including inorganic salts Sulfates are not absorbed so readily as chlorides and their presence in the intestines stimulates intestinal secretion, which accounts in a large part for their cathartic effect The solubility of calcium magnesium and phosphorus and of iron and other metals is greatly affected by the acidity of the intestinal contents the rate of absorption depends on the solubility of the substance The rate of absorption of calcium and phosphorus also appears to be altered by the presence or absence of vitamin D The administration of this vitamin so alters the permeability of the intestine that more calcium and phosphorus are absorbed absorption is impaired when a deficiency in vitamin D exists The permeability of the intestine for absorption of iron apparently depends on the reserve of iron in the body When the body contains adequate stores of iron, only traces of iron are absorbed from whatever large amounts may be administered, if deficiency of iron is present the absorption of iron is greatly increased

Digestive and absorptive functions of the intestine are not completely quiescent during fasting There is a continuous flow of water and of all substances from the plasma into the intestine, as there is into all tissues of the body Reabsorption of this material may amount to as much as 15 per cent of the ordinary daily dietary intake This has been shown with fat When rats which ordinarily eat about 1 gm of fat daily, are fasting or are fed fat free diets, they continue to absorb fat and the intestinal lymph always contains more fat than is present in the blood Absorption of vitamin K continues during fasting and complete drainage of intestinal lymph will rapidly produce deficiency in prothrombin in the fasting animal

In addition to its digestive and absorptive functions, the mucosa of the small intestine may alter substances during absorption It synthesizes new substances from the end products of digestion and from substances withdrawn from the circulating blood Fatty acids fed in pure form appear in the lymph from the intestine as glycerides and phospholipids Some fatty acids differing from those fed also appear in the glycerides and phospholipids of the lymph The amount of cholesterol in the intestinal lymph is also increased by feeding fat, although no cholesterol is contained in the diet When free cholesterol is fed it appears in the intestinal lymph already esterified by its passage through the intestinal mucosa Some synthetic processes also continue in the intestine during fasting as can be shown with phospholipids and cholesterol Absence of pancreatic juice from the intestine depresses this synthesis probably by interfering with absorption of fat during fasting

Absorption from the Large Intestine.—Absorption from the large intestine appears somewhat similar to absorption from the small intestine. Water and all of the products of normal digestion may be absorbed from the large intestine. Under ordinary circumstances the amount of this absorption is small, most of the material available is absorbed in the small intestine, only small amounts in low concentration reaching the large bowel. Bacterial action is most intense in this part of the gut, and it is here that the products of that action are absorbed. If large amounts of carbohydrate or protein reach the large intestine either as a result of the failure of absorption in the small intestine or as a result of rectal administration, bacterial action frequently gives rise to the formation of excessive gas and also of certain toxic substances. Some of the products of bacterial action are very irritating to the large bowel and interfere with the absorptive processes. Bacterial action seems to be the chief obstacle to rectal feeding. But water, glucose, amino acids, sodium chloride, and soluble vitamins may be given in this way. Maximal absorption is obtained when the solution administered is of such concentration and given at such rate that the unabsorbed excess or residue will not be subjected to prolonged bacterial action.

SUMMARY

The maintenance of normal nutrition depends, in general, upon three things: (1) food, which contains in one or another utilizable form all the basic substances required for growth and repair of body tissues and energy for the production of heat and mechanical activity, (2) the gastrointestinal tract, which, functioning properly, prepares the food for entrance into the body tissues and fluids, and (3) the metabolic mechanism by means of which the absorbed substances are employed in the tissues of the body. This summary deals with the second of these.

The most conspicuous general physiologic characteristic of the gastrointestinal tract and the associated glands having a part in the process of digestion is the wonderful coordination of the essential mechanisms. Such mechanisms are both motor and inhibitory and are initiated and controlled by both nervous and hormonal factors as well as by substances made from the ingested food.

The process of digestion begins with the secretion of saliva and the trituration of food in the mouth. When the bolus of food is passed into the esophagus, voluntary control over it ceases and is not again exercised till the indigestible part of it is ready to be ejected. The chief functions of the stomach are (1) to store ingesta, (2) to permit salivary digestion to proceed for a longer period than otherwise would be possible, (3) to secrete hydrochloric acid and pepsin, which furnish one of the two important mechanisms for digesting protein, and (4) to secrete an enzyme for coagulating certain foods, such as milk, in the young and so, by making it more difficult for those foods to leave the stomach, give more opportunity for gastric digestion to occur.

Passage of the ingesta through the stomach depends upon many factors, the most important of which are the physical and chemical characteristics of the food itself and the motor mechanism of the stomach. Liquid foods

pass through the stomach in a short time If the food is solid, the motor mechanism of the stomach is required to expel it into the duodenum The movements of the stomach are quite complex They are weak and shallow in the fundic wall, where they tend simply to adapt the size of the stomach to the amount of material it contains, and are strong and vigorous in the pyloric region whence they sweep the gastric contents into the duodenum The mechanism responsible for evacuation of the stomach is also quite complex and both nervous and humoral mechanisms are involved The pyloric sphincter should not be considered the only important factor controlling passage of the gastric contents into the duodenum, for the whole pyloric region is involved in the emptying of the stomach It should be noted that the movements of gastric digestion and evacuation are very orderly, with the result that the ingesta are passed into the duodenum in a condition and at a rate suitable for the proper functioning of the intestine

After passing into the intestine the chyme is propelled caudally by waves of peristalsis mixed and brought into contact with the intestinal mucosa by segmentation movements Peristalsis consists of waves the progress of which is marked by localized relaxation followed by more localized contraction Peristaltic waves are of two types (1) slowly moving contractions proceeding for only short distances in the intestine and (2) swift movements sweeping without pause for long distances The segmentation movements re localized contractions that isolate short segments of intestine and mix he materials contained in them These movements are of two types, regular nd irregular, depending upon whether the rate and amplitude are constant not

Gastric secretion occurs in three progressive phases These are dependent on different types of stimulation of the gastric glands The first or phalic phase is due to a nervous mechanism set in operation by the environmental factors associated with taking food the second or gastric phase to both mechanical and chemical stimuli within the stomach, the third or intestinal phase to chemical agents probably secretogogues, originating in the intestine

The digestive secretions in the small intestine come from three sources—the pancreas the liver and the intestinal mucosa The pancreas and the intestines are made to secrete by both nervous and hormonal mechanisms The factors causing the secretion of bile are not understood but appear to be correlated with activities of the digestive tract

The digestive enzymes may be divided into two groups according to the kinds of mediums they require for optimal action Pepsin requires an acid medium all the other enzymes a neutral or slightly alkaline medium Most of the acid secreted by the fundic mucosa is buffered or neutralized by the food The acidity also diminishes slightly as the gastric contents pass through the pyloric region of the stomach though the reaction of the chyme here is usually acid The principal mechanism for altering the reaction of the gastric contents from acid to alkaline is encountered just beyond the pylorus There are three main factors in this mechanism (1) the bile, which acts mainly as a diluent (2) the pancreatic secretion which dilutes, buffers and neutralizes the acid and (3) the duodenal and intestinal secretions, the action of which is similar to but to a considerable degree less than that

of the pancreatic secretion These various mechanisms are so carefully coordinated that the pH of the intestinal contents from distal area to duodenum is acid for only very short periods

The chemical processes of digestion accomplish the degradation of the complex organic molecules of ingested foodstuff into simpler, smaller, more soluble, and more diffusible molecules This process not only reduces the food to molecules capable of passing through the intestinal mucosa into the blood and lymph but also makes material for the resynthesis of proteins and fats characteristic of the recipient rather than of the source of food Digestive processes in hydrolysis are accomplished by specific enzymes having their greatest activity at body temperature and at the pH of their usual intestinal environment Without enzymes, hydrolysis of the same food in a test tube requires strong acids or alkalis at boiling temperature The digestive enzymes are very specific, apparently because each substance has a molecular contour that must be fitted specifically by the contour of its digestive enzyme There is some evidence that the gastrointestinal tract develops enzymes in proportion to the specific foods continually taken in the diet Some substances, such as cellulose, are digested only by bacterial action in the intestine, which cannot be trained to develop digestive enzymes of the sort just mentioned

Absorption of digested food from the intestine is an efficient process, only a small portion of utilizable food is excreted in the feces Most of the absorption occurs in the small intestine, though some absorption occurs in other parts of the gastrointestinal tract All the known physical laws of membranes and substances in solution play a role in absorption from the intestine In addition, the intestinal mucosa possesses specific properties enabling it to pass substances into the blood at rates other than would obtain by operation of purely physical laws The absorption of dextrose may be aided by phosphorylation in the intestine Fat may be absorbed in combination with phosphate in the form of phospholipids and also in combination with bile salts, which may combine with fatty acids to pass them through the intestinal mucosa There is considerable evidence to indicate that the absorption of many substances depends upon the condition of the intestinal mucosa Iron is absorbed from the intestine when the body stores of iron are depleted, but only small amounts are absorbed when those stores are adequate Inefficient absorption such as occurs in the absence of the pancreatic juice and perhaps in certain vitamin deficiencies, appears to be due to alteration in the condition of the intestinal mucosa The absence of bile in the intestine interferes with the absorption of both fats and fat-soluble vitamins

A wide variety of experimental procedures have been used to alter motor mechanism, secretion, digestion, and absorption in the gastrointestinal tract And section of nerves, surgical alteration of the gastrointestinal tract, removal of the stomach, duodenum, colon, or large parts of the jejunum and ileum, exclusion of the bile and of the pancreatic juice have some effect on the efficiency of the gastrointestinal tract One is impressed, however, by the paucity of effects these precedures have and continues to wonder at this mechanism which is able to take foods of all types under extreme conditions and yet supply the body with its needs

The gastro-intestinal tract continues to function even when it is deprived of food A considerable amount of fat diffuses from the blood into the intestine during fasting This is reabsorbed by processes similar to those of the absorption of food Several synthetic processes such as the formation of phospholipids and the esterification of cholesterol, take place in the intestinal mucosa These processes also continue at a somewhat reduced rate during fasting

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Chapter 3

The Hormonal Control of Metabolism

By Mary E Dumm and Elaine P Ralli

INTRODUCTION

Intermediary metabolism can be viewed as a series of reactions by which solar energy, originally stored in carbohydrate by the process of photosynthesis in green plants is made available to animal cells to do physical, chemical and osmotic work This is true even when the animal cell uses fatty acids or amino acids as a source of energy, since both of these foodstuffs are formed ultimately from glucose, either by plants or animals

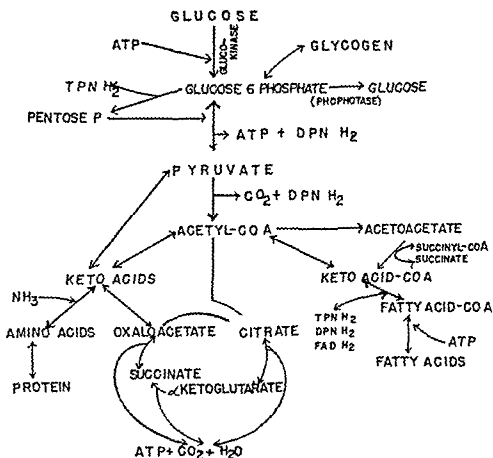


Fig 3 —Outline of reactions of intermediary metabolism

Conversely the anabolic aspects of metabolism are reaction sequences in which the cells utilize a part of the energy released in catabolism to do chemical work Molecules of higher energy level (and usually of higher

molecular weight) are formed from substrates of lower energy level. The synthesis of fatty acids from the intermediates of carbohydrate metabolism is an example of such a process.

The actual mechanisms by which hormones influence metabolic reactions are still largely unknown and are in some cases matters of considerable controversy. However, the fact that directly or indirectly hormones can exert striking effects on the direction and magnitude of certain metabolic processes is beyond question. Even so it seems clear that hormones are not absolutely necessary for the occurrence of metabolic reactions. Unicellular organisms and cells in tissue culture metabolize and multiply without any dependence of hormonal regulation at least as it occurs in the "higher" animals. Animals from which all known endocrine glands have been removed surgically can live without hormone therapy although precariously, providing that their environment, both external and internal, is carefully controlled.

Before discussing the influence of hormones on metabolic reactions the main pathways by which carbohydrate, fat and protein are utilized by living cells will be briefly described. No attempt will be made to present in detail the complex transformations which the foodstuffs undergo or to described the enzymatic mechanisms by which these changes are accomplished. Rather the reader is asked to notice their mutual interdependence. Some of the reactions discussed are outlined in Figure 3.

THE METABOLIC PATHWAYS OF THE MAJOR FOODSTUFFS

Carbohydrate Metabolism.—The monosaccharides are carried in the blood as the free sugars (*e.g.* D glucose). The initial reaction in the metabolism of glucose is its phosphorylation to glucose 6 phosphate, a reaction in which the terminal phosphate of adenosinetriphosphate (ATP) is transferred to glucose with a loss of the energy of the high energy phosphate bond in the ATP. This reaction is catalyzed by a phosphokinase, hexokinase (also referred to as glucokinase). Glucose 6-phosphate can be reversibly converted to glycogen in both liver and muscle with the release of inorganic phosphate. Glycogen can be reconverted to free glucose in liver, but not in muscle, due to the presence in the liver of the necessary phosphatase which converts glucose-6-phosphate to glucose.

There are least two alternate pathways for the further metabolism of glucose-6-phosphate. The first is the Embden-Meyerhof (glycolytic or anaerobic) pathway in which two triose phosphates are formed, both of which can be oxidized to pyruvic acid with the production of energy as ATP (Fig. 3). The hydrogen removed in the oxidative step is transferred to DPN (diphosphopyridine nucleotide) to form reduced DPN (DPN H_2). Under anaerobic conditions pyruvate is reduced to lactate and the DPN H reoxidized to DPN. The overall effect is the anaerobic conversion of glucose to pyruvic or lactic acids with the release of a small part of the energy potentially available in glucose.

The alternate pathway in carbohydrate metabolism is an oxidative pathway sometimes known as the hexosemonophosphate shunt. The oxidative shunt provides a mechanism for the oxidation of glucose-6-phosphate one

carbon atom at a time, starting with C_1, with the production of CO_2 and reduced TPN (TPN H_2) (triphosphopyridine nucleotide) The pentose phosphates formed from glucose 6-phosphate are split into smaller metabolites which recombine to form fructose-6-phosphate, an intermediate in the Embden-Meyerhof pathway Since fructose-6-phosphate is readily converted to glucose-6-phosphate, the oxidative shunt can be viewed as a cyclic process bypassing the Embden-Meyerhof pathway

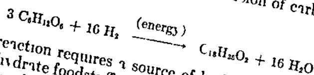
All of the reactions from glycogen to pyruvic acid are reversible in the sense that the organic molecules involved can all be converted either to glycogen or to pyruvic acid However, in reactions involving large changes in free energy (*e g*, phosphorylation by a phosphokinase) the participation of different enzymes is necessary, depending on the direction in which the reaction is proceeding The formation of glucose and inorganic phosphate from glucose-6-phosphate, for example, requires a phosphatase, the formation of glucose-6-phosphate from glucose requires a glucokinase and ATP and involves a loss of energy

The pyruvic acid which was formed in the Embden-Meyerhof pathway can be completely oxidized in the Krebs citric acid cycle (tricarboxylic acid cycle) In order to enter the cycle the pyruvate is first decarboxylated to acetyl-CoA by a rather complex reaction sequence requiring lipoic acid, thiamine pyrophosphate, DPN, coenzyme A and Mg^{++} Acetyl-CoA is an important and versatile metabolite which is concerned in many processes other than the oxidation of the carbohydrates Acetyl-CoA enters the citric acid cycle by condensing with oxaloacetate to form citrate In the course of passing once around the cycle the equivalent of 1 molecule of acetate is completely oxidized, and oxaloacetate is resynthesized The immediate products of the oxidation of the acetate moiety are CO_2 and hydrogen in the form of the reduced pyridine nucleotides (*e g*, DPN H_2) The formation of H_2O from the hydrogen of the reduced pyridine nucleotides plus molecular oxygen takes place in several steps and is coupled to the formation of the high energy bonds of ATP This process is the source of the major part of the energy available to the cell

Monosaccharides other than glucose can also form glycogen or be oxidized to CO_2 and H_2O with the production of energy as ATP Fructose can be phosphorylated in the liver and also to a limited extent in muscle to form fructose-6-phosphate which is readily converted to glycogen or to lactic acid Galactose is phosphorylated in the liver to galactose-1-phosphate, which can be converted to glucose-1-phosphate, and so to glycogen or glucose

Lipid Metabolism —The oxidation of the fatty acids requires, first, their activation to fatty acid-CoA derivatives, a reaction requiring ATP as a source of energy Subsequently, the fatty acids are broken down, two carbon atoms at a time, to produce acetyl-CoA and acyl-CoA derivatives containing two less carbon atoms than the original fatty acid In the process, reduced pyridine nucleotides and flavoproteins are formed The subsequent oxidation of the acetyl-CoA produced from the fatty acids is apparently identical to that of acetyl CoA produced in carbohydrate metabolism, and again is the means by which the major part of the energy available in fats is released to the cell

It has been known for many years that fatty acids are continually being broken down and resynthesized and that carbohydrate can be converted to fatty acids. The overall reaction in the conversion of carbohydrate to fat can be summarized as follows



$$3\ C_6H_{12}O_6 + 16\ H_2 \xrightarrow{\text{(energy)}} C_{18}H_{36}O_2 + 16\ H_2O$$

Basically this reaction requires a source of hydrogen and also a source of energy if carbohydrate foodstuffs (about 4 calories per gram) are to be converted to fatty acids (about 9 calories per gram). It appears that fat synthesis depends upon carbohydrate metabolism in three ways: (1) to provide the necessary hydrogen in the form of the reduced pyridine nucleotides (DPN H^2 and TPN H^2); (2) to provide the necessary energy in the form of ATP, and (3) as a source of the carbon chains which are reduced to fatty acids.

When carbohydrate metabolism is depressed the oxidation of the fatty acids becomes the major source of energy for the cells. Under these circumstances acetyl-CoA may be produced more rapidly than it can be utilized. When acetyl CoA accumulates acetoacetic acid is formed which leads to the development of ketosis. The defect in the utilization of acetyl-CoA may be related to a relative lack of the carbohydrate intermediate oxaloacetate, which condenses with the acetyl CoA to form citrate. Acetoacetic acid can be reincorporated in the general metabolic pathways only by being reactivated by the formation of acetoacetyl-CoA. This reaction can occur in extra hepatic tissues with succinyl-CoA, an intermediate of the citric acid cycle, as an activating agent. Consequently the removal of acetoacetic acid is aided by reestablishing carbohydrate metabolism which will lead to increased production of both oxaloacetate and succinyl CoA.

Protein Metabolism.—While the primary and essential functions of amino acids in the diet are related to growth and to the synthesis of substances required by the cells such as enzymes, amino acids can also serve as a source of energy. The details of the interconversions of the amino acids are outside of the scope of this chapter. However there are certain rather general statements we can make about their utilization by the cells. Usually the first step in the oxidation of an amino acid is its deamination to form the related keto acid. The deamination may take the form of the transfer of an amino group from one amino acid to another keto acid already formed. Ultimately the carbon chains of most of the amino acids can be converted either to pyruvate, to α-ketoglutarate or to acetyl CoA. In the first two cases, the amino acids can be considered glucogenic, that is, the carbon chain can form glycogen or glucose. However when the carbon chain of an amino acid forms acetyl CoA, that amino acid is ketogenic and will not increase the total carbohydrate intermediates available to the organism.

Examination of the reactions indicated in Figure 3 shows that carbohydrate, fatty acids and amino acids can be regarded somewhat as the spokes of the wheel centering on the production of acetyl CoA at the hub of the wheel. The major release of energy from all these metabolites occurs when the acetyl CoA is completely oxidized in the citric acid cycle. In general when metabolic reactions proceed out from acetyl-CoA to glycogen

fatty acids or protein, some source of energy is required in order for these syntheses to take place. If the production of acetyl-CoA from one source decreases, for example from carbohydrate, a compensating increase in acetyl-CoA production from another source, for example from fatty acids, occurs. Minor adjustments of this type can be made readily. However, a major adjustment leads to distortion in the balance of the wheel, as a whole, and impairment in other aspects of metabolism, for example impairment in energy production, in synthetic reactions, and in acid base balance.

METABOLIC EFFECTS OF THE HORMONES

The following survey of the metabolic effects of the hormones will be limited to vertebrate animals, particularly mammals. Invertebrate and plant hormones will not be included. After summarizing what is known of the influence of the hormones on metabolic processes, the interrelation between the nutritional state of the animal and the action of the hormones will be discussed.

Insulin.—The injection of crystalline insulin, the hormone secreted by the β cells of the pancreas, is followed by a prompt lowering of blood sugar. In an animal deprived of insulin by surgical removal of the pancreas, or by treatment with alloxan, blood sugar rises, liver glycogen becomes depleted, the synthesis of fatty acids from carbohydrate is impaired, and ketone bodies tend to accumulate. If insulin is administered to such an animal the metabolic picture is gradually restored to normal. A similar although less acute, disturbance occurs in fasting and in individuals fed a high fat, low carbohydrate diet.

In spite of the fact that insulin has been used therapeutically for more than twenty-five years, and although the amino acid sequence of insulins from several species has been elucidated,[1,2] the actual mechanism by which insulin exerts its effects is still unknown. In the absence of insulin, all forms of glucose utilization are impaired in isolated tissues and probably also in the whole organism (*i.e.*, conversion to glycogen, conversion to fatty acids, oxidation to CO_2 either in the citric acid cycle or the oxidative shunt, and the rate of turnover of the mucopolysaccharides[3,4]). However, in the diaphragms of alloxan-diabetic animals fructose can be oxidized at normal rates.[5] Taken together, these facts suggest strongly that a primary locus of action of insulin is in the conversion of circulating blood glucose to intracellular glucose-6-phosphate, a biochemical impairment which would be expected to result in a widespread disturbance in glucose, but not in fructose metabolism. Whether the effect of insulin is on the glucokinase reaction, as such, as originally suggested by Price, Cori and Colowick[6] or on the transport of glucose across the cell membrane, as proposed by Levine *et al.*,[7] still cannot be decided with confidence. Other possible mechanisms have also been proposed but will not be discussed here.[8,9]

Although the most obvious early signs of insulin lack are hyperglycemia and glycosuria, the fact that severe disturbances in fat metabolism also occur with insulin deficiency has long been recognized. The accumulation of acetone bodies and the frequent occurrence of fatty livers in patients with untreated diabetes mellitus are both indicative of a disturbance in fat

metabolism. In experimental animals deprived of insulin, an impairment in the synthesis of fatty acids from carbohydrate is well established.[5,10,11] Recently it has been shown that the level of the non-esterified fatty acids (NEFA) in the plasma is elevated in diabetic human subjects especially those in ketosis, and decreases following the injection of insulin.[1] At present the available data suggest that the effect of insulin on fatty acid metabolism is probably indirect and a consequence of the effect of insulin on carbohydrate metabolism. The impairment in fatty acid synthesis which is observed with insulin lack may be prevented when carbohydrate utilization is maintained by such means as feeding fructose.[13] The need for both reduced pyridine nucleotides and for ATP provides a reasonable basis for the dependence of fatty acid synthesis on carbohydrate metabolism since TPNH, DPNH and ATP are all produced in the reactions of carbohydrate metabolism and probably required in the conversion of acetyl-CoA to fatty acids.[14]

Insulin influences protein metabolism although probably indirectly. The administration of insulin is associated with an increased rate of amino acid incorporation into protein.[15,16] In the absence of insulin and also in fasting the rate of amino acid breakdown and consequently nitrogen excretion is increased. The increased amino acid breakdown is associated both with the increased gluconeogenesis which occurs when carbohydrae metabolism is depressed and with the oxidation of the carbon chains of the amino acids as a source of energy.

The action of insulin has been studied extensively *in vitro* as well as *in vivo*. Insulin when added to the rat diaphragm increases glucose uptake, glycogen synthesis, conversion of isotopically tagged glucose to CO_2 and to fatty acids. The response is sufficiently reproducible to have been widely used as an assay for the insulin activity of the plasma and as a tool to detect the presence of insulin antagonists.[17-20]

The *in vitro* effects of insulin on adipose tissue have been widely studied. Direct effects of insulin have been reported in adipose tissue for glucose uptake, glycogen synthesis, oxidation of substrate to CO_2 and incorporation of substrate carbon into fatty acids.[21,22] This tissue has been used to estimate the insulin activity of such fluids as blood plasma. In less extensive experiments insulin *in vitro* has been reported to influence the carbohydrate metabolism of mammary gland tissue[3] and human leukocytes.[4,4a]

It is still uncertain whether alterations in liver metabolism in diabetes are a direct result of insulin lack or an indirect result of the effects of insulin on the peripheral tissues. Liver slices from alloxan-diabetic rats deprived of insulin for relatively long periods are not responsive to insulin added *in vitro* although the diaphragms from the same animals are insulin-responsive. Even when the insulin was injected and the rats sacrificed at varying intervals after receiving therapy six to twelve hours had to elapse before the rate of phosphorylation of glucose and the rate of synthesis of fatty acids were significantly increased. These observations led to the tentative conclusion that insulin probably did not exert any direct effect on liver metabolism, and that the deranged liver metabolism was an indirect consequence of responses elsewhere in the body to the diabetic state.[5,6] However more recent data indicate that early in the insulin deficient state

there is little difference between the liver and the diaphragm of the alloxan diabetic rat in their response to injected insulin.[27]

With the availability of isotopically labeled glucose, studies on the effect of insulin *in vivo* on glucose removal and glucose production have been undertaken in a number of laboratories. Some of this work has been done in connection with studies of the action of the sulfonylurea drugs. Perhaps because of differences in procedures, these investigators are at present far from agreement. Data from several laboratories suggest that under physiological conditions the outstanding effect of insulin *in vivo* is a decrease and even a complete suppression of glucose production by the liver.[28,29] Other investigators interpret their results as indicating that the primary effect of insulin on carbohydrate metabolism is to enhance glucose removal by the tissues. In their view, changes in the rate of glucose production by the liver are of minor importance in blood sugar regulation by insulin.[30–32]

It is perhaps unfortunate that in the majority of studies of the effects of insulin administration *in vivo*, the hormone was injected peripherally. Endogenous insulin is secreted directly into the portal circulation and thus reaches the liver before it can possibly affect the extrahepatic tissues. Studies in which arteriovenous differences in glucose concentration have been compared after the peripheral and after the portal injection of insulin have indicated that a substantial part of the insulin administered intraportally is probably removed by the liver.[33] The fact that a hormone is removed by or concentrated in a particular organ does not, of course, prove that this organ is an important site of action of the hormone. In the case of the hepatic removal of insulin, the possibility of destruction of the hormone in the liver, perhaps by insulinase, must also be considered.[34] It is of interest that the presence of an enzyme actively destroying insulin in liver tissue might account for the frequent failure to demonstrate direct *in vitro* effects of insulin in liver slice experiments.[6]

At present it seems impossible to decide either the biochemical mechanism of insulin action or the relative importance of insulin effects in the liver and in the peripheral tissues. Other aspects of the influence of insulin on metabolic processes which are not discussed here are (1) alterations in the activity of enzymes in diabetic animals and patients, particularly glucose-6-phosphatase (to be discussed under *Effects of Hormones on Enzymes*), (2) the activity of insulin and insulin antagonists in blood plasma,[3,17–20] (3) insulin binding by various tissues,[2] and (4) comparison between the effects of insulin and sulfonylurea drugs.[2,35]

Epinephrine.—Epinephrine (adrenalin) and norepinephrine (noradrenalin) are the hormones produced and secreted by the adrenal medulla. In addition to their metabolic effects they have a striking influence on vasomotor activity and on the muscular and central nervous systems. Only the metabolic effects will be reviewed here.

It is probable that epinephrine plays an important part in the regulation of blood sugar concentration. Epinephrine (and norepinephrine in much larger doses) causes hyperglycemia, glycosuria and a decrease in the glycogen content of the liver and muscles. One factor controlling the rate of secretion of epinephrine is the level of blood sugar. Providing the splanchnic nerves are intact, a fall in blood sugar, induced for example by the in-

jection of insulin will be followed by a release of epinephrine and an increased output of glucose from the liver.[36] Conversely the injection of glucose particularly in the region of the hypothalamus leads to a decreased secretion of epinephrine.[37]

The secretion of epinephrine also plays some part in the release of corticotrophin (ACTH) from the anterior pituitary. Both the injection of epinephrine and stressful stimuli leading to its secretion by the adrenal medulla are associated with an increased secretion of ACTH which, in turn causes the release of the corticosteroids from the adrenal cortex.[38, 39] It is uncertain whether the effect of epinephrine is directly on the anterior pituitary or mediated through the hypothalamus.[40] However, the fact that the injection of epinephrine is normally followed by evidences of increased secretion of corticosteroids is well established.

There is considerable evidence that the effect of epinephrine (and also of glucagon) on the output of glucose from the liver is due to an enhancing effect of the hormone on the production of active phosphorylase. Phosphorylase is an enzyme which degrades glycogen to glucose-1-phosphate with inorganic phosphate as a required participant in the reaction



$$(C_6H_{10}O_5)_n + n\ H_3PO_4 \longrightarrow nC_6H_{11}O_6\ H_2PO_3 \text{ (glucose 1 phosphate)}$$

Liver, heart and muscle all contain enzymes which inactivate phosphorylase and reactivating systems which reform active phosphorylase. The amount of active phosphorylase is increased following the injection of epinephrine[41] *and also when the hormone is added to liver homogenates*[4] *Other investi*gators have shown that the nature of the cationic environment can influence that rate of inactivation of phosphorylase.[43] A puzzling aspect of this problem is why the glycolytic but not the glycogen synthesizing activity of the tissue is increased by an elevated level of active phosphorylase since *in vitro* the reaction is reversible. One possible explanation is the hypothesis proposed by Niemeyer[44] that *in vivo* phosphorylase may function exclusively as a glycogen degrading enzyme with a different system employed for glycogen synthesis. The report by Leloir and Cardini[45] of the biosynthesis of glycogen from uridine diphosphate glucose by a liver enzyme system is strong support for this suggestion.

Epinephrine added *in vitro* also inhibits glucose uptake by muscles. The mechanism of this effect is unknown. It has been suggested that glucose-6-phosphate may accumulate as a result of the glycogenolytic effect of epinephrine and inhibit hexokinase.[46] Data contradicting this hypothesis have also been reported.[47] The actual importance of this effect of epinephrine on glucose uptake *in vivo* is unknown.

The physiology and pharmacology of epinephrine and norepinephrine have been recently reviewed.[48]

Glucagon.—Glucagon, originally known as the hyperglycemic factor of the pancreas has been extracted and crystallized from pancreatic tissue where it is believed to originate from the α cells.[49] A glucagon-like material has also been purified and isolated from pancreatic vein blood.[50] Hyperglycemic extracts have also been obtained from a number of other tissues particularly the gastric mucosa. However, their identity with glucagon remains to be established. The complete amino acid sequence of hog glucagon

has been reported[51,5] It is a straight-chain polypeptide containing twenty-nine amino acid residues and with a minimum molecular weight of 3485. The occurrence of glucagon in crude insulin preparations and in pancreatic vein blood, plus the fact that purified glucagon has a hyperglycemic effect, has led to the inference that glucagon is in some sense an anti-insulin hormone. However, its actual physiological role remains to be established. When glucagon is injected intravenously, the blood sugar rises and the glucose-1-phosphate and glucose-6-phosphate contents of the hepatic cells increase. The action of glucagon in the liver is similar to that of epinephrine, that is, it is glycogenolytic and increases the level of active phosphorylase (see section on Epinephrine). Glucagon is also effective in increasing active phosphorylase in cell-free liver homogenates.[53] Studies of the effect of glucagon in cell-free systems have led to the suggestion that glucagon increases liver phosphorylase in two steps: (1) the formation of an active factor, perhaps adenine ribonucleotide, by a particulate fraction of the homogenate and (2) the effect of the active factor on the phosphorylase system either by enhancing the formation of active phosphorylase or inhibiting its inactivation.[5]

In addition to the effect of glucagon on liver glycogenolysis, which is well established, effects of glucagon on other tissues and organs have been reported.[5?] These include a reduction of gastric and pancreatic secretion, and intestinal motility, and in human beings, a feeling of hunger satiety. In the kidney glucagon has been reported to enhance electrolyte excretion. While there is general agreement that, in contrast to epinephrine, glucagon has no effect on muscle phosphorylase, glucagon in low concentrations has been reported to enhance glucose uptake in muscle and to increase slightly the peripheral utilization of glucose. The overall effect of glucagon on liver glycogen levels actually is conditional on dosage and the availability of other hormones. The infusion of relatively large doses of glucagon leads to depletion of liver glycogen stores. However, chronic treatment with small doses actually increases liver glycogen providing both adrenal corticosteroids and insulin are also available.

Several review articles on the biochemistry and metabolic effects of glucagon have recently been published.[5,54,55]

Growth Hormone.—Growth hormone has been obtained by a number of chemical methods from the anterior pituitary. It is a protein hormone, the amino acid sequence of which is only partially known.[56,57] The various types of growth hormone preparations are not identical with one another either in chemical or biological properties, and the possibility of the presence of biologically active contaminants cannot be entirely excluded.[58]

Growth hormone has well recognized effects on carbohydrate, protein and fat metabolism. In carbohydrate metabolism, growth hormone has anti-insulin effects and is sometimes described as diabetogenic. It produces glycosuria and hyperglycemia in normal cats and dogs, and permanent diabetes in subtotally depancreatized dogs and cats. A part, but not all, of the hypersensitivity of hypophysectomized animals to insulin is due to the absence of growth hormone. However, the complete restoration of normal insulin sensitivity and glucose tolerance depends on treatment both with growth hormone and with the corticosteroids.[58,59]

In spite of the fact that growth hormone has effects antagonistic to insulin under some circumstances, under others growth hormone acts synergistically with insulin and may actually increase its secretion, possibly as a response to the increased levels of plasma glucose.[58–60] In studies with radioisotopes, the administration of growth hormone to hypophysectomized dogs has been reported to cause an increase in glucose production by the liver and also to increase glucose outflow from plasma to the tissues. In these same studies, the rate of glucose turnover in the untreated hypophysectomized dogs was lower than normal.[61]

Data suggesting that growth hormone stimulates the secretion of a hyperglycemic factor from the pancreas have been reported.[6] However these observations have been questioned by others and present evidence does not warrant the conclusion that an important part of the hyperglycemic effect of growth hormone is due to an increased secretion of glucagon.[58]

The biochemical locus of action of growth hormone is unknown. Two effects on the enzymes of carbohydrate metabolism have been postulated. Anterior pituitary extract has been reported to inhibit the hexokinase reaction,[6] and purified growth hormone added *in vitro* to rat diaphragm has been reported to exert a respiratory quotient depressing effect by blocking the conversion of hexosediphosphate to pyruvate.[63] Other investigators have not obtained any consistent response to the *in vitro* addition of growth hormone to rat diaphragm.[58] However, the injection of growth hormone has been reported to lead to the formation of a lipoprotein in the serum which has an inhibitory effect on the response of rat diaphragm to insulin added *in vitro*.[64,65]

In addition to the effects on carbohydrate metabolism, growth hormone has a well defined action on protein anabolism. At present there is no uniformity of opinion as to whether the primary effect of growth hormone is to decrease protein catabolism, to increase protein synthesis, or both, although it is evident that treatment with the hormone can result in an increase in the body nitrogen content of fed animals.[58] An adequate dietary source of protein is necessary if this effect is to be fully manifest. In animals treated with growth hormone nitrogen excretion is decreased, and it has been reported that the total amount of plasma proteins increased. Demonstration of this effect is also dependent on adequate amounts of insulin. The effect of insulin on protein metabolism, which was noted earlier, may be due to this synergistic response.

Protein deposition in the tissues under the influence of growth hormone is accompanied by a loss of fat. At the same time there is a marked decrease in the respiratory quotient, suggesting that a greater oxidation of fat occurs under these circumstances. Injection of growth hormone is associated with a mobilization and transport of fat from the tissues to the liver and an increase in ketone body formation. The ketogenic effect of growth hormone is dependent on the presence of the liver and on adrenocortical and thyroid hormones. Whether the effect of growth hormone is primarily an increased fatty acid breakdown or an inhibition of fatty acid synthesis cannot be decided with the evidence available at the present time.[58]

The chemical properties and the metabolic effects of growth hormone have been reviewed recently.[56–58]

Adrenocorticotropic Hormone (Corticotropic) (ACTH).—ACTH has no direct effect on intermediary metabolism so far as is known at present. Its importance is related to the fact that it stimulates the secretion of the corticosteroids from the adrenal cortex. Consequently, the metabolic effects of its administration are those of the corticosteroids, which will be described below.

The corticotropins are well-characterized chemically. The amino acid sequences of preparations from several species have been established.[66–68] In all cases (pig, beef, sheep), the active unit contained thirty-nine amino acids with what appear to be very minor differences in amino acid sequence.

Adrenocorticosteroids.—The 11-oxysteroids (cortisone and hydrocortisone) of the adrenal cortex are synthesized and secreted from the adrenal cortex in response to stimuli from the pituitary mediated by ACTH. The biosynthesis and subsequent metabolism of these substances have both been extensively studied and recently reviewed.[69,70]

Adrenalectomized animals develop hypoglycemia readily on fasting and are hypersensitive to injected insulin. The injection of the corticosteroids into normal, hypophysectomized or adrenalectomized animals is followed by an increase in blood sugar concentration and an increase in nitrogen excretion.[71,72] While there is little doubt that one effect of the corticosteroids is to enhance gluconeogenesis, it is not certain that the hyperglycemia is entirely due to the conversion of amino acids to glucose in the liver. Both an inhibition of the peripheral effects of insulin on glucose utilization and an inhibition on lipogenesis from carbohydrate have been reported to contribute to the hyperglycemic effect of these substances.[73,74] However, evidence tending to contradict the peripheral effect of corticosteroids on glucose utilization and on lipogenesis has also been reported.[75]

There are several recent studies of the effect of the adrenocortical hormones on the metabolism of isotopically-labeled amino acids. When adrenal cortical activity was increased the excretion of urea nitrogen also increased. This increased urea nitrogen consisted both of labeled nitrogen from the tagged amino acids and unlabeled nitrogen presumably derived from protein catabolism. Incorporation of the labeled amino acid into the carcass proteins has been reported decreased by the cortical steroids and incorporation into hepatic proteins increased. A possible interpretation of the data would be that the corticosteroids stimulate increased catabolism of the tissue proteins leading to increased mobilization of amino acids to the liver where both increased protein synthesis and increased urea formation occur.[76]

Thyrotropin (TSH).—Thyrotropin (TSH) is a protein hormone from the anterior pituitary which stimulates the thyroid gland to release its hormone. Highly active preparations of TSH contain some carbohydrate suggesting the possibility that thyrotropin may be a mucoprotein.[77] The secretion of TSH is influenced by the level of circulating thyroid hormone and may also be under the influence of the hypothalamus.[78] Pituitary stalk section usually results in decreased thyroid function and increased thyroid activity has been reported after electrical stimulation of the hypothalamus. Radioactive thyroxine is concentrated in certain regions of the hypothalamus,

suggesting that changes in blood levels of thyroxine may influence TSH output by an action on the hypothalamus rather than by a direct effect on the anterior pituitary

Thyroid Hormone —The thyroid hormone is stored in the thyroid gland as the metabolically inert thyroglobulin The most abundant circulating form of the hormone is the free amino acid thyroxine, which is bound to the α-globulins Thyroxine is released from thyroglobulin by cathepepsins, the activity of which is enhanced both *in vivo* and *in vitro* by TSH [79]

Recent work has led to the identification and synthesis of other substances with thyroid activity [80] Triiodothyronine has been identified in extracts of thyroid tissue[81] and in plasma of hypothyroid patients treated with thyroxine where it is also bound to the α globulins Triiodothyronine has also been identified in liver and kidney preparations to which thyroxine was added *in vitro* Clinically, triiodothyronine is highly active and usually gives a somewhat more rapid response than thyroxine This and similar evidence has led to the suggestion that the triiodothyronine is the peripherally active form of the thyroid hormone and that it is produced by deiodination of thyroxine in the tissue cells

The activity of a number of other analogues of thyroxine has been investigated [80] The most interesting are the acetic acid analogues of thyroxine and triiodothyronine Both compounds increase the metabolic rate in rats and produce an immediate rise in oxygen consumption when added to rat kidney slices [8] These results have not been confirmed in all respects by other investigators [83] Since thyroxine and triiodothyronine increase oxygen consumption in tissue slices only after a latent period it has been suggested that both substances may have to be converted to the acetic acid analogue in order to influence tissue respiration

The administration of the thyroid hormone is associated with increased oxygen consumption some impairment in glucose tolerance, a decline in plasma cholesterol, and an increase in creatinine excretion which is probably related to weight loss The thyroid hormone is necessary for normal growth and development and will induce metamorphosis in amphibian larvae Hypothyroid individuals tend to have low metabolic rates, impaired carbohydrate absorption from the gut and often retain salt and water Of the various physiological effects of the thyroid hormone, the most intensively studied at the cellular level is its effect on oxygen consumption Both thyroxine and triiodothyronine decrease the efficiency of the production of high energy phosphate bonds, in other words the ratio of high energy phosphate formed to oxygen consumed (P/O ratio) is decreased when thyroxine or triiodothyronine is added either to tissue slices or to mitochondria [84, 8] Thyroxine also causes structural changes in liver mitochondria both *in vitro* or *in vivo* and this effect can be prevented *in vitro* by Mg^{++} or Mn^{++} and is accentuated by Ca^{++} [86–89] At present this data is intrepreted as indicating that thyroxine causes a labilization of the structure of the mitochondria and that this structural change in turn influences oxidative phosphorylation In discussing this problem, Hoch and Lipmann[90] have pointed out that in normal cells the mitochondria are under a degree of thyroid influence, and that partial uncoupling of oxidative phosphorylation is necessary if synthetic reactions are to proceed smoothly Hydrogen

is required for biosynthesis and cannot be entirely utilized in oxidative phosphorylations if hydrogenations are to keep pace with other types of synthetic reactions.

Androgens.—In addition to the effects of the androgens on the secondary sex organs, these substances have a protein anabolic effect on the tissues generally and promote nitrogen retention in the intact animal. The anabolic effect may be related to the observation that kidney slices from animals injected with testosterone incorporate isotopically-labeled glycine into the cells more readily than kidney slices from control animals.[91]

Effects of Hormones on Enzymes.—In spite of the extensive information available concerning the chemistry and physiological effects of hormones, the mechanisms by which they influence metabolic processes are not known. Of the various hypotheses considered, one of the most widely discussed is that hormones exert their effects by participating in, or by regulating, the activity of some enzyme system. This effect might be produced by controlling the level of accelerating or inhibiting substances.[9] While there are extensive data showing that changes in enzymatic activity do occur in response to changes in hormonal levels, there is no certainty that the primary action of a hormone necessarily involves an enzyme system.[93,94]

It is generally recognized that some of the alterations in enzyme activity which occur are probably secondary in nature and represent responses on the part of the cell to the changed metabolic situation induced by the hormone.[94] For example, the level of glucose 6-phosphatase is elevated in depancreatized and in alloxan-diabetic animals and can be brought back to normal values by treatment with insulin.[95,96] A similar increase in glucose-6-phosphatase occurs when a direct source of glucose is excluded from the diet,[97] although under some circumstances a secondary adaptation occurs in which the elevated level of glucose-6-phosphatase later declines to normal values.[98] Present data suggest that a high level of glucose-6-phosphatase is induced by a low level of glucose utilization and has the effect of increasing glucose production by the liver. This effect might reasonably be supposed to contribute to the hyperglycemia of diabetes mellitus.

Another example of an enzyme whose activity may be the result of a metabolic adaptation to a condition induced by the level of hormonal activity is tryptophan peroxidase. The activity of this enzyme is enhanced by fasting[99] and by treatment with cortisone[100,101] and is decreased by adrenalectomy.[99] The enzyme level is also increased by the administration of tryptophan.[99] While it is by no means certain that the formation of the enzyme is dependent on the level of tryptophan at the enzyme-forming sites in the liver, it is suggestive that both fasting and treatment with cortisone lead to increased protein catabolism and, therefore probably to increased availability of tryptophan. It is less easy to explain the fact that insulin also increases tryptophan peroxidase levels since insulin tends to decrease protein catabolism.[99]

The investigations that have been reported do not justify any definite conclusions as to the means by which hormones induce secondary changes in the level of enzymes. They do suggest that under some circumstances an

alteration in nutritional factors available to the cells may result in, and contribute to, alterations in cellular enzyme levels

THE INFLUENCES OF NUTRITIONAL SITUATIONS ON HORMONAL ACTION

Introduction.—Metabolic reactions are conditioned by many factors, among which are the availability to the cells of the major foodstuffs, the effect of hormones on cellular reactions, and the effect of the nutritional situation within the cell on its enzymatic components. Deprivation of the major foodstuffs such as is seen in malnutrition may not be due solely to a lack of food but may result from impaired absorption from the intestinal tract as in colitis, from loss of available nutrients because of diarrhea or polyuria, or from a lack in the diet of essential nutritional factors resulting

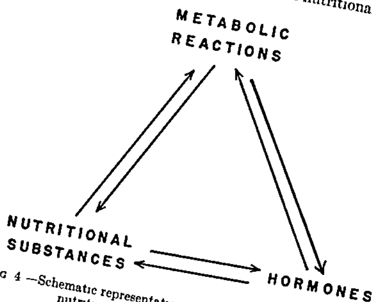


FIG 4.—Schematic representation of the influence of hormonal and nutritional factors on metabolic reactions

in a specific deficiency. Situations which deprive the cells of essential nutrients may interfere with the synthesis of hormones. In addition, the various hormones may by their actions further disturb the nutritional situation within the cells. The interaction of these factors is illustrated in Figure 4 which emphasizes the influence of these reactions on each other. Metabolic reactions are continuous and can be disturbed by abnormalities or deficiencies at any point in their cycle.[102]

The Effects of Malnutrition on the Pituitary Hormones.—Malnutrition deprives the cells of calories and foodstuffs and thus alters cellular function. The pituitary gland is particularly sensitive to nutritional deficiencies and this interferes with the synthesis of its hormones.[103] For example, the synthesis of the pituitary hormones is decreased when the diet is deficient in protein. Under these circumstances the end organs remain physiologically intact and will respond to the administration of a tropic hormone such as

ACTH.[104] Sheehan's syndrome[105] illustrates the increased sensitivity of the anterior pituitary cells to loss of blood at the time of delivery. The adrenal glands are smaller than normal in malnourished patients and show evidence of lipid depletion, due to lack of ACTH. It is also reported that the excretion of the 17-ketosteroids is diminished in undernourished subjects. Starvation is associated with a decreased synthesis of the gonadotrophic hormones,[103] as has been shown in both world wars and in countries where famine has occurred. Zubiran and Gomez-Mont[104] have reported that ovaries from chronically malnourished patients were, in many instances, small or atrophic and functional ovarian bodies could not be detected.

The secretion of other pituitary hormones, such as thyrotropin, may also be depressed and this is evidenced by morphological alterations in the thyroid gland, such as atrophy, involution and degeneration.[103, 104]

Experiments have been done on the response of malnourished animals to the injection of many of the pituitary hormones. A consistent finding has been the lack of effect of growth hormone in animals on diets low in calories, proteins or certain vitamin fractions. The retardation of growth observed in undernourished children may be due in part to the decreased synthesis of growth hormone and in part to the ineffectiveness of this hormone when the essential nutrients are lacking in both quantity and quality.

The Effects of Nutritional Situations on the Hormonal Action of the Endocrine Glands.—The vitamins function metabolically principally because of their role as part of the various coenzymes. In discussing the relation of vitamins to the action of the hormones of the endocrine glands, two situations are considered: (1) the effect of vitamin deficiencies on the condition and function of some of the endocrine glands, (2) the effects of changes in endocrine activity on nutritional requirements.

1. *The Effect of Vitamin Deficiencies on the Condition and Function of Some of the Endocrine Glands.*—The various endocrine glands appear to have specific needs for certain vitamin fractions. The adrenal gland is particularly sensitive to a deficiency of either pantothenic or ascorbic acid. Morgan[106] originally observed that a deficiency of the "filtrate factor," later identified as pantothenic acid, caused lipid depletion, atrophy, necrosis and often hemorrhage of the adrenal cortex. These pathological changes were associated with evidences of a disturbance in the physiological function of the adrenal cortex. Deficient animals subjected to natural stress or injected with ACTH did not show the decrease in the number of lymphocytes and eosinophils characteristic of normal animals,[107] although the response could be elicited by cortisone.[108] When pantothenate-deficient fasting animals were subjected to the stress of anoxia or injected with ACTH, liver glycogen did not increase as it did in normal adults.[109] An increased sensitivity to insulin was also observed in pantothenate-deficient animals.[108] Adrenal-cholesterol concentrations decreased in these animals and its restoration following stress was delayed.[110, 111]

The ascorbic acid content of the adrenal gland is quite high and is depressed when the gland is stressed. Deficiency of this vitamin will also affect the structure of the adrenal cortex, causing atrophy and other changes somewhat similar to those produced by a deficiency of pantothenic acid. Factors regulating the exit and entrance of ascorbic acid in the adrenal

gland may reflect modifications in the cellular oxidation reduction systems which are important in adrenal steroidogenesis The exact role of ascorbic acid in this respect is obscure but Jones *et al*[11] reported that moderate ascorbic acid deficiency in the guinea pig sufficient to produce some of the symptoms of scurvy but prior to weight loss does not significantly modify elaboration or metabolism of the 17 oxycorticosteroids

Two recent reports indicate some relationship between vitamin A metabolism and the adrenals Clark and Colburn[113] studied the conversion of carotene to vitamin A in the rat and found that cortisone-treated rats were unable adequately to convert carotene to vitamin A An elevated serum carotene level has been reported in patients with diabetes and in patients with myxedema and in these patients carotenemia is a common finding Rosenberg and Sobel[114] found a decreased synthesis of vitamin A in the gut of alloxan treated rats indicating that lack of insulin may also be related to the normal metabolism of carotene

The ovarian glands are sensitive to deficiencies of almost all of the fractions of the vitamin B complex Many years ago Evans and Bishop[115] reported that rats deficient in vitamin B ovulated infrequently if at all Deficiency of thiamine will also produce this condition In 1944 Drill and Burrill[116] noted that if the caloric intake of a complete ration was restricted to the amount equivalent to that consumed daily by animals fed a vitamin deficient diet reduction in ovarian activity cessation of the estrous cycle and gonadal dysfunction resulted Vitamin E is also extremely important for normal ovarian function Lack of this vitamin causes sterility in the rat Male rats show a loss of motility of the spermatozoa and irreversible damage to the germinal epithelium occurs later in the deficiency[117] Recent investigations suggest that vitamin E participates in electron transport systems and its physiological effects may result from disturbances in these systems[118-120] Pyridoxine-deficient rats do not maintain a normal pregnancy but it has been found that approximately 25 per cent of such animals can maintain their pregnancies if anterior pituitary gonadotropins are given to the animals and 80 to 100 per cent if the ovarian hormones are used[1] The evidence suggests that both the pituitary and the ovaries are affected by a deficiency of pyridoxine This vitamin is the prosthetic group for a number of enzymes that remove carboxyl groups from amino acids transfer amino groups from one compound to another and remove sulfhydryl groups from sulfur containing compounds Whether this has a bearing on its role in maintaining ovarian function is not known

At the present time there is very little evidence that the pancreas or insulin are dependent on nutritional factors However the fact that obesity depresses carbohydrate tolerance suggests that the action of insulin may be influenced by the accumulation of the body stores of fat and this may be due to some disturbance in fatty acid metabolism During periods of starvation the incidence of diabetes is sharply reduced indicating again that the effect or the sensitivity of the cells to insulin depends in some way on fat metabolism

Vitamins and amino acids are involved in the synthesis of thyroxine[122] and atrophy of the thyroid gland has been reported in diseases such as cirrhosis of the liver in which a marked protein deficiency exists[123] Vitamin

B_6, because of its role in a variety of transformations of the amino acids, is particularly involved in the formation of the protein hormones

2 **The Effects of Changes in Endocrine Activity on Nutritional Requirements** —As was pointed out earlier in this chapter, hormones can exert striking effects on the direction and magnitude of certain metabolic reactions Although metabolic reactions will proceed in the body in the absence of almost any one of the hormones, the speed of these reactions is very much depressed when certain hormones are lacking Therefore, either an increase or decrease in the release of hormones will be reflected in cellular metabolism and will affect the cellular requirement for certain vitamins and other essential nutrients A striking example of this is the effect of an increase in the thyroid hormone as is seen in hyperthyroidism In this condition, the caloric needs of the body are greatly increased due to the elevated metabolic rate There is an increased requirement for almost all of the water soluble vitamins It has been shown that vitamin B_1 deficiency[124] will occur more rapidly in rats that are receiving the thyroid hormone while on a deficient diet When the amount of the thyroid hormone is depressed with resulting myxedema, the absorption of foodstuffs across the intestinal mucosa is interfered with The conversion of carotene to vitamin A is depressed There is an increased sensitivity to insulin, hypoglycemia is quite a common finding, and there is a disturbance in fat metabolism which is reflected in an increase in the cholesterol level in the serum

When insulin is lacking, as in the patient with diabetes mellitus, there is also an increased requirement for the water soluble vitamins, as these are excreted in greater amounts than normal because of the polyuria Riboflavin deficiency is seen in the patient with uncontrolled diabetes, and peripheral neuritis was so common prior to the administration of vitamin B_1 to these patients that it was known as "diabetic neuritis"

In conditions of stress, according to Selye,[125] the response of the organism involves the stimulation of the adrenal cortex by ACTH Under these conditions increasing amounts of the adrenal steroids are excreted The capacity of the body to respond to stress can be conditioned by a variety of nutritional factors There are certain vitamins which appear to increase the ability of the animal to withstand the demands created by cold stress Among these is ascorbic acid, which has been reported as improving the response of rats and monkeys exposed to cold[126,127] Large amounts of pantothenate will increase the ability of rats to swim in cold water[128] Rats fed a diet consisting of 10 per cent dried liver powder will also be able to swim longer in cold water[129]

That the condition of the tissue cells is the critical factor in the response of the animal to stress has been shown by studies on adrenalectomized rats[128] Animals and men deprived of their adrenal glands are particularly sensitive to any kind of stress However, young adrenalectomized rats receiving very large amounts of pantothenate in their diet were able to swim for long periods in cold water[130] Other vitamins are also reported as being important in the ability of rats to withstand exposure to cold These are pyridoxine,[131] riboflavin,[132] vitamin A,[133] and vitamin B_{12}[134] Thus it seems clear that hormonal effects can be modified by nutritional substances

PRINCIPAL METABOLIC DISEASES ASSOCIATED WITH HORMONAL IMBALANCE

The process of living inevitably requires adaptation to environmental physiological and pathological situations and consequently alterations in endocrine activity are continuous. Under certain circumstances the endocrine disturbances may be great enough to result in diseases of the endocrine system. The outstanding diseases of the endocrine system involve the pituitary gland, the thyroid, the pancreas and the adrenals. In diseases involving the endocrine glands because of the associated metabolic disturbances the function of the liver is often encroached upon and the associated alteration in liver function may exaggerate the physiological effects of the disease.

The effects of diseases of the endocrine glands are greatly influenced by the age of the individual at the time the disorder occurs. This is particularly true in diseases of the pituitary gland. For example before puberty an increased secretion of the growth hormone causes gigantism whereas after puberty an increased secretion of this hormone results in acromegaly. The age of the individual also influences the complications that result from endocrine diseases. The adolescent patient with hyperthyroidism does not suffer from the vascular complications which occur in patients in the older age group whose cardiovascular system is less able to withstand the stress of the disease.

Most diseases of the pituitary are associated with tumors among which the outstanding are the chromophobic tumors. These tumors are usually associated with loss of the posterior pituitary hormones causing diabetes insipidus. Tumors of the anterior pituitary affect principally the basophilic or eosinophilic cells. A tumor of the eosinophilic cells is characterized by an overgrowth of body tissues and is known clinically as acromegaly. This disease also is associated with a disturbance in carbohydrate metabolism and about 75 per cent of the patients have diabetes mellitus. Tumors involving the basophilic cells result in the syndrome known as Cushing's syndrome which is characterized by hirsutism, hypertension, stimulation of the gonads, changes in protein metabolism with thinning of the skin and a disturbance in carbohydrate metabolism evidenced by an increased blood sugar following meals.[135] Atrophy of the pituitary glands such as was described by Simmonds[136] produces results similar to those observed in the hypophysectomized animal. Gonadal function is decreased, early aging is a prominent symptom, adrenal cortical insufficiency may occur and hypothyroidism and low metabolic rates are also present.

Diseases of the thyroid gland may be associated with either an increase in the secretion of the thyroid hormone resulting in the clinical condition of hyperthyroidism, or a decrease in hormone production resulting in hypothyroidism. This latter condition when profound results in myxedema.[137]

The outstanding disease of the pancreas is diabetes mellitus. In this disease there is a block in the metabolism of carbohydrate due either to a lack of insulin, to an interference in the action of insulin or to a decreased sensitivity of the cells to the effects of insulin. The recent observations of

the effects of the sulfonylurea drugs on blood sugar levels in patients with diabetes emphasized the complexity of the problems affecting the endocrine glands and their hormones The release or the effectiveness of insulin can apparently be influenced by these drugs It is not unlikely that in the future other substances, some of which may be nutritional, will be found which will condition the action of hormones on cellular reactions

One of the well-known diseases of the adrenal cortex is Addison's disease [138] The outstanding physical findings are the pigmentation present in apparently 75 per cent of the cases, low blood pressure, low fasting blood sugar low serum sodium and elevated serum potassium The disease is associated with changes in carbohydrate and protein metabolism and electrolyte balance The effects of the disease can be counteracted by administration of adrenal cortical steroids

Another disease of the adrenal is associated with tumors of the adrenal cortex These tumors result in an oversecretion of the adrenal cortical hormones and a condition known as the adrenogenital syndrome occurs In this disease the metabolic disturbance is evidenced by retention of salt and water hypertension and hyperglycemia [139]

SUMMARY

The diseases involving the endocrine glands illustrate the importance of the interrelations of hormonal, metabolic and nutritional factors in the control of intermediary metabolic reactions in patients Inevitably in diseases of the glands of the endocrine system, a disturbance in the function of one gland will affect the others Equally important to remember is the fact that disturbances in the endocrine system affect the nutritional situation in the patient and consequently alter the requirements for the various nutrients It is more realistic therefore, experimentally and clinically, to consider metabolic, nutritional and endocrine disturbances as interrelated parts of a general disturbance The data presented in this chapter point to the interlocking effects of nutritional and endocrine factors on metabolic interrelations

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Chapter 4

The Psychology of Appetite

By Henry W Brosin

HUNGER AND APPETITE

Physiologists, in studying the activities of the gastrointestinal system, have found it valuable to distinguish between hunger and appetite Hunger may be recognized by two components The first is a generalized weakness which may be related to sensory nerve impulses from the alimentary canal, and perhaps occasionally to lowered blood sugar [12, 13]

The second component is a more definite perception in the epigastric region, consisting of intermittent sensations of tension or pressure of brief duration These hunger pangs are usually associated with appetite but may be independent of it The physiological basis for hunger contractions appears to be inherited with relatively little modification from the experiences of the individual These contractions have a fixed pattern (thirty minutes activity with one and a half to two hours rest) which does not vary markedly whether the period of abstinence from food is prolonged or short A starving man will become weaker but not more uncomfortable It is said that a man can live without food for five weeks but cannot survive lack of water more than five to ten days Hunger of this type is stopped by solids in the stomach even though they may not be highly nourishing The mechanism of the hunger contractions is not clearly understood They are not dependent upon the extrinsic motor nerves, because they are evident even after these nerves to the stomach are cut Blood sugar level may be a factor but contractions may occur while the contents of the last meal are still in the stomach

Appetite, while often accompanying hunger, may be present without it One may want to continue eating an excellent meal long after hunger has been satisfied The components for appetite are principally psychological and are the result of the past experiences of the individual We learn to like and dislike foods from our earliest days, and often these patterns are thoroughly fixed in adult life The nature of the memories associated with the early ingestion of food will determine preferences in a manner independent of logical considerations, and hence will be puzzling to the physician who is attempting a rational therapy for a patient with nutritional problems If we remember the old adage about there being no disputing matters of taste or the wide variations in diet among the various nations of the earth, it will be easier to tolerate the food vagaries of our patients

THE INFLUENCE OF HEREDITY

The interest in hereditary bulimia which began with Danforth's work on yellow mice in 1927 has greatly increased with new work on other mammals.[14]

While studies of heredity in human obesity cannot be pursued under as rigorous conditions as in laboratory animals there are a number of careful projects which reinforce the thesis that the constitution or the physical characteristics (shape and size) of the body are inherited but the amount of adipose tissue is not. The more convincing of these human studies are on identical (monozygotic) twins, because it is believed that such pairs are identical for all body traits. If there is a body-weight variation, it is presumably due to environmental, including psychological, factors. It was, in fact, found by von Verschuer in 1927 and Newman *et al* in 1937 that the weight of identical twins varied more significantly than any other anthropologic measurements.[5,48] The differences in weight tended to be 2 to 3 times as great as the other trait variations. This was especially true for identical twins living apart under dissimilar conditions.

So again we find that the evidence from human genetics compels us to examine in closer detail the nature of environmental factors influencing appetite and habits of eating.

RELATIONS OF TASTE AND ODOR TO APPETITE

Traditionally, physiologists and psychologists both have studied the sense organs and their relation to the total central nervous system. Progress in the visual and auditory spheres has been tremendous compared to that in the chemical senses.[22]

Adrian's electrophysiologic research in the chemical senses has enabled him to find characteristic shapes on a photographic reproduction of the discharge obtained from leads off the mitral cell layer of the olfactory bulbs. Substances such as xylol, pyridine and eucalyptus, when present in the air can be identified by the curves on the record.[1]

"Although Adrain hesitates to conclude that the brain identifies the smell by the same criteria he states that it would be easy on this basis to see how a great variety of smells might be distinguished without the need for very great variations in the receptors. If this is so Adrian feels that it would be possible to relate olfactory discrimination both to auditory and to visual discrimination. Tones are distinguished by the general regions of the basilar membrane which are excited; visual scenes by the detailed patterns. Smells seem to be distinguished by a combination of detailed pattern and general region. But when all this is clear, the central problem of the nervous system will still be to explain how the spatio temporal patterns of incoming discharges are dealt with by the brain.[60]

At this time we cannot expect the sensory physiologist to help us with problems at the psychological level of integration. The sensory psychologist is only gradually learning to measure the four tastes bitter, sweet,

sour, and salt Perception of a taste involves, in addition, odor, touch, and temperature Appetite probably also involves the state of hunger (including the emotional state), the appearance of the food, and previous habits of eating The voluminous literature on these problems gives us very little help in understanding why some people have either hypo- or hyperphagia The factors governing food intake appear to be related principally to the total organization of the individual rather than to the anatomy or the functional efficiency of the 9,000 taste buds on his tongue or the nerve pathways conducting the impulses to the brain The far reaching possibilities of an odor triggering a complex series of chemical and physiological activities resulting in a clinical attack of bronchial asthma is reported in 22 patients by Stein and Ottenberg [44] If more corroboration for such sequences is found, new dimensions will be added to the understanding of the influence of odor upon appetite and upon other body functions

Investigation of the chemical senses includes continued studies on racial and sex or other group differences, and on many other types of individual differences While many of the studies do not throw much light on the large problems of appetite as they concern the physician, it might be of interest to report the follow up work in human subjects testing the now well-known work of Richter on rats, which may be of importance to the demand feeding concept in children

Ever since the pioneer work by Davis in 1928 on self-selection of diet, permitting "newly weaned infants to choose their own foods in such quantities as they may desire from a fairly wide range of commonly used natural food materials," there has been a keen interest in this subject Her conclusions on 3 subjects, 2 of which were observed for six months each, and 1 for twelve months, are "They were able from the first to select their own foods from a list of simple natural ones and in quantities sufficient to maintain themselves with apparent optimal digestive and good (as far as immediate results could be judged) nutritional results They were omnivorous and in eating were governed not only by their caloric needs, but showed definite preferences, which however changed from time to time and were unpredictable "[15]

Aldrich and Hewitt carried on this experiment with 668 infants and found that 92 per cent of the babies had excellent appetites Only 1 per cent had some type of anorexia, while 7 per cent were borderline [23]

There is a vast literature on all aspects of child feeding which need not be considered here except that these very early disorders of eating raise the obvious question as to whether these infants are the ones who in adult life will have severe personality conflicts I do not know of valid follow-up studies, but this hypothesis needs extensive investigation in view of the many variables which may alter unduly simple conclusions and recommendations The central importance of the psychological components in feeding and other bodily processes has been one of the most significant advances in recent pediatric practice and has resulted in increased recommendations for the return to breast feeding and closer mother-child relations in the hospital [34, 43]

Richter's experiments supported the hypothesis that receptor sensitivity is lowered with need, he used the preference threshold as a measure of

sensitivity.[8-31] Meyer tested the same hypothesis by examining the change in the threshold for glucose in human subjects as they underwent food deprivation.[4] Nine subjects, deprived of food for thirty-four hours, were measured nine different times during the experiment for their threshold to glucose and also to two control substances, sodium chloride and quinine bisulfate. At the end of the starvation, they ate freely and the thresholds were measured again. The effects of deprivation were found to be insignificant for the group although there were large differences among subjects. Consequently Richter's hypothesis that there is increased intake of appropriate substances with need is not substantiated and a new explanation seems in order.

LEARNING THEORY

There is insufficient evidence at this time from the early years of life of an individual to permit much more than enlightened guesses on the various factors governing the formation of appetite, food preferences and dislikes, and the use of food as an equivalent for other activities. Among leading psychologists we may cite Tolman's work as an example of an attempt to incorporate appetite into a unified learning theory. He regards appetite as a construct akin to demand differentiation and biases which are intervening variables in addition to his basic "sign Gestalt expectation" which is the hypothetical learning change. These intervening variables are to be defined in terms of independent experimental conditions. They would include external environmental factors as well as variables in the subject person. In order to describe human behavior it would be necessary to work with even more complex intervening variables. These latter are further displaced toward the final behavior and they depend not only upon certain independent variables but also upon combinations of various of the preceding 'first line' and 'second line' variables.[47]

The experiments using simple conditioning methods in relation to human appetite do not reveal any new or useful data for the understanding of disorders of eating.

INSTINCT THEORY AND APPETITE

In most common sense definitions of appetite as well as in textbook discussions there is a recognition that while many components of appetite are dependent upon learning or environmental factors there remains a basic component which is deeply grounded biologically and therefore may be called a primary need to preserve life or an instinct. There are numerous instinct theories but the view presented by Kubie in 1948 is chosen for presentation because he comes to grips with some of the real difficulties in all instinct theory, while trying to utilize the best insights from modern neurophysiology, psychology and psychoanalysis, in order to describe as nearly as possible an objective concept of the function of the biological drives. Since it is difficult to do justice to this carefully constructed essay in an abstract form it is recommended for firsthand reading.[27]

> 'Instincts represent the demand which the body makes on the mental apparatus. . . . There are no absolute distinctions between instincts and drives

The nucleus of each is a neuronal pattern which is partly inherited and partly acquired and modified through learning and conditioning. The instincts can be ranged in order in an hierarchy of increasing complexity. In this hierarchy there is a gradual shift from a preponderance of biochemical influences on the neuronal pattern to a preponderance of psychologic influence. In varying proportions both types of forces operate on the central neuronal pattern of every instinctual process and their relative roles will be different in different species.

"There is no such thing as a simon pure instinct, devoid of psychologic forces. In this hierarchy, in order of complexity, are respiration, water balance and maintenance of tissue substance (all vital to the biochemistry of the individual), with a widening temporal separation of the intake and output phases in water balance and tissue maintenance so as to produce two separate groups of instinctual derivatives. The secondary instincts serve to maintain not the individual but the species and involve increasing complexity and lengthening intervals, and consequently greater susceptibility to psychologic elaboration and distortion. The third order of instinctual processes has to do with the general level of neuromuscular activity which operates primarily to implement and support all instinctual acts and secondly determines the general level of alertness and of total neuromuscular activity, and the aperiodic cycle of sleep and wakefulness, of aggression and submission.

"These are seen to operate in normal psychology as in psychopathology. The relative roles of the three components of instinctual activity vary in different instincts and in different species. In many of the instinctual processes the biochemical source of energy is converted into behavior through deprivation, because deprivation synchronizes the continuous asynchronous flux which in states of rest goes on in body tissues. The biochemical processes, however, are linked to warning mechanisms which under ordinary circumstances come into play before any actual tissue deprivation occurs. Therefore in higher animals instinctual patterns are triggered off by warning mechanisms rather than by tissue hungers. Therefore on the psychologic level, instinctual aims and objects are also built around the warning mechanism."[22]

These passages bring into focus the possibilities of a coordinated theory of behavior that gives adequate prominence to both the physiological and psychological components. It avoids the errors of oversimplification which occur by listing trait names which do not help explain behavior, and also detours around the artificial problems inherent in attempting to identify "primary" needs and "derived" needs since the three levels described form a continuous spectrum.[4]

APPETITE AND THE UNCONSCIOUS

As we progress in our study of concepts of instinct theory and motivation we are forced to find ways of dealing with those forces or components of the total motivation that are unknown to the person himself. Many of these can be detected by a trained observer with the possibility of inferring relationships between his current overt behavior, the hidden material, and the characteristic action patterns of the patient. Following the extraordinary discoveries of Freud (1856–1939) it has become common to call these forces "unconscious." Freud's concepts have been both illuminating and

productive in understanding in a common sense manner the ways in which a person's motivations influence his behavior It should be said that the concept of an active unconscious has many difficult semantic and theoretical problems inherent in it but in spite of this it is at present the most valuable conceptual tool for our task of explaining human behavior, in all its complexity in intelligible psychological terms [4]

Miller identifies 16 different definitions for the word "unconscious" and cites case histories which illustrate the varied uses [4] In this chapter we will use the concept in its Freudian framework

APPETITES AND CONFLICT

When basic needs or drives in the altered forms are frustrated there results conflict Every child must undergo training in mastering more or less his need to find gratification immediately This is sometimes an arduous task, for some children seem to have a very strong appetite that is not easily denied or the techniques for repressing it are not strong enough to curb it, or perhaps they are not helped adequately to develop the controls necessary Children or adults who are too freely indulged in some or all of their wants are said to be spoiled Civilization demands some self-restraint or self-denial from all of us in order to make possible the achievement of more complex activities that permit us to become reasonable adults who can work at a job with industry and skill and assume the responsibilities of living in a family and a community Those who do not acquire minimal controls may become involved with the law they may become accident-prone or suffer from rages convulsions or a panorama of somatic disorders with more or less neurotic or psychotic processes

The complexity of the disorders of appetite in an adult can be better understood against this background for it is common knowledge that "just as the twig is bent the tree's inclined," so we know that all the activities which surround the acts of eating from the time of birth form much of the basic substrate of a man's character If a child is reared in an atmosphere where it must constantly fight for the food it gets and never be certain that the food will appear even though strenuous measures are taken to obtain it one can understand the basic insecurity pessimism and doubt which may be a constant residue in adult life even though food is now plentiful The child who is always hungry will not be easily persuaded at a later date that it need not be concerned because food is now easily available

If the hunger of the child becomes associated with the amount and timing of the human affection it receives, as seems to be the case in many patients we have the psychological precondition for later mood disorders In adult life it appears that there are many persons hungry for love, friendship, lights music gaiety prestige, power and renown far beyond ordinary bounds of material needs and ambitions Many such persons achieve marked success by virtue of unusual talent and industry, yet with all the evidence of worldly success including money fame and admirers find themselves insatiable in their continued demands to be loved even more

If the need to be loved is not met within limits the resulting frustration may cause more overt efforts to gain their objective or the frustration when

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unrelieved will cause depressive tendencies which may manifest themselves physiologically, psychologically, or socially, or in any combination of these three Such depressive feelings can be combatted by myriad devices which will be developed from time to time in answer to varied current needs by virtue of the antecedent patterns which have proved useful in the past, the basic physiological organization of the organism, and current available methods of defending itself against the unhappy sense of loss or separation If no outlets seem available, the person may become apathic, withdrawn, and anorexic with some resemblance to the starved, marasmic children described by Spitz and Bowlby [6 7 37–42] Some depressive persons overeat as a means of providing for themselves the outward visible evidence that they are loved and cared for While insomnia is characteristic of many depressions, because the sufferers are unable to resolve their inner debate at night, it is also true that some depressed persons are able to still the inner conflicts sufficiently to indulge themselves in sleep, and therefore present a picture of hypersomnolence

Some physicians who work long hours at night have themselves experienced the equivalence between sleep and food as they find themselves revived by food in going from one sick patient to another without sleep Other ways in which mildly depressed persons fight their inner mood is to engage in sporadic vigorous activity in their work, social activity, sports, charities, committees, hobbies, reading, radio, and television viewing The latter may be thought of as a visual equivalent of oral intake This activity, even though it is at times forced or frenetic may provide a mask of normal activity which successfully eludes detection and only elicits defensive jeers when it is mentioned Inordinate courting of hazards in driving fast motor cars, dangerous ice-boating, skiing or mountain climbing may likewise not be detectable as ways in which a depressive mood is combatted unless one has a very intimate knowledge of the person's inner feelings If a person uses alcohol or other drugs immoderately or employs such social devices as quarreling, fighting, or other destructive methods to relieve his inner tension, then the family and colleagues are more apt to notice it and may mention it to the physician

to get what they want. They are doomed to failure in much of this because seldom can they find anyone who can give them what they want. "Without giving any consideration to the feelings of their fellow men they demand of them an understanding of their own feelings. They are always bent upon establishing a good understanding with people, though they are unable to fulfill their own part of such an understanding; this need compels them to attempt to deny their ever present readiness to react hostilely."[17] This brief summary of one underlying pattern of motivation will help our understanding of some of the eating disorders, and the steps essential for their correction.

PARTIAL STARVATION STATES

Including Reducing Regimens

If any one of the physical systems of the body is put under sufficient stress it would be expected that the entire organism would show signs of this pressure. Schiele and Brozek report the "semistarvation neurosis" which resulted from food deprivation in a controlled experimental study on 36 healthy young male volunteers. The semistarvation changes common to the entire group are summarized as follows: "The chief psychologic manifestations which were found characteristically in all subjects are intense preoccupation with thoughts of food, emotional change tending toward irritability and depression, decrease in self-initiated activity, loss of sexual drive and social introversion."[33]

These findings are of interest to physicians who prescribe reducing diets (inducing semistarvation states) because it is usually helpful, and sometimes absolutely essential, to find means by which the patient can channel his tensions into other activities which are meaningful to him in his fight to eat less. It is a paradox that while a patient is attempting to lose weight his psychological state is that of semistarvation. A good example of the dynamics of so-called equivalence is that found frequently between smoking and eating. Numerous men found themselves eating more and gaining weight up to 40 pounds when they stopped smoking. It is well known that others use smoking and drink alcohol as a barrier to eating.

Among the drugs that are offered as useful in weight reduction diets are those of the amphetamine series. It is uncertain how much specific anti-appetite action there may be in these compounds although this action is claimed for them. It is notable that these compounds assist some people in achieving better spirits, a more energetic outlook and a larger sense of well-being. Consequently they are recommended for use in mild depressive states where the action will be variable depending on the strength of the inner conflicts. If too large amounts are taken the patient may feel in-creased tension and anxiety although some of the newer compounds re-duce undesirable side effects considerably. Unfortunately many patients soon find ordinary dosages inadequate to curb their appetites, and this can be understood in terms of the dynamics involved. The use of tension-reducing drugs with or without the further aid of familiar sedatives such as bromides, barbiturates or opiates can only be of minor assistance to the ...tal need of the patient for adequate "intake." This "intake" may be

conceived of as being nutritional, pharmacological or psychological To variable degrees, depending on the total system balance, some of these "intakes" have substitutive value In a gross form it can also be seen in the treatment of alcoholism by the use of some form of the *Rauwolfia serpentina* or *chlorpromazine* compounds for disturbed emotional states These powerful agents will act on the biological organism in the desired direction of sedation but this is merely symptomatic treatment which brings some grateful temporary relief but does not reach the nuclear problem A cocktail in a friendly social gathering may help cheer a man up but it will not help him get the money to pay household bills, nor pacify the boss who is threatening him Chemical obtundation will not resolve the patient's strong appetite although it may become a partial source of supplies to those who need them The story of alcoholism in its manifold grades is a familiar one which can serve as a guide to the physician who is working on a constructive therapeutic regimen The success of Alcoholics Anonymous and similar clubs for obese persons can also point the way to finding more socially acceptable activities for the patient with a severe eating disorder

In the Minnesota experiments on semistarvation "excessive gum chewing was *one of the reactions that may be considered as an 'inefficient'* mechanism It was started in an attempt to alleviate hunger and nervous tension, but it was continued compulsively in spite of the fact that it failed to give the desired result This symptom occurred in great intensity *in four subjects, two of these failed to adhere to the semistarvation diet* "[9]

Although all subjects showed more or less "semistarvation neurosis" which was relieved by feeding, 9 subjects showed either unusual or exaggerated grades of symptoms which are worth reporting

> "Two men suffered from paresthesias of probable physiologic origin One had sensory and motor disturbances, probably hysterical in nature Another subject suffered from a psychogenic accident In 4 men the reaction to the *stress took the form of a character neurosis The disintegration manifested itself* by inability to adhere consistently to the diet Under the moral and social pressures to conform to the experimental regimen, one of these 4 developed a pathologic reaction bordering on psychosis, this cleared rapidly upon his release *from the experiment* "[33]

With these examples in mind we can now look to those cases of self-induced anorexia and hypophagia with a better perspective regarding both the etiology and the treatment

ANOREXIA AND HYPOPHAGIA

Following the publication of Simmonds' paper on pituitary cachexia in 1914, there developed an extensive literature upon the differences between this syndrome and that described by Sir William Gull as anorexia nervosa [19 36] Gradually, after much hard work, the basic problems in nutrition and endocrinology became sufficiently clear to understand that self-induced starvation may cause severe cachetic states and death [18] The demonstra-

tion by Sheehan in 1939 that true Simmonds' disease was due to post-partum necrosis of the anterior pituitary helped resolve the problem.[25] It did not give any more insight than possessed by Gull in his brilliant paper on young girls who do not eat.

The accumulation of patients who have been studied psychiatrically furnishes evidence which enables the physician to detect the chain of psychological events which lead to hypophagia. Sylvester describes one girl aged three and one-half years whose critical condition due to self induced severe weight loss was accompanied by stuporous withdrawal negativism, and mutism. This regressive state related to inadequate love from the mother was successfully treated in the hospital by psychological methods which are described by Sylvester. It has been pointed out repeatedly that in treatment of children of essential importance is the actual living through a relationship with a person whose attitudes are different from those of the original pathogenic parent.[46] The treatment of a four-year-old girl weighing only 23 pounds with symptoms of anorexia and vomiting again shows the need to repair the regressive processes of infantile withdrawal.[4] The psychodynamics of this child were quite similar to those described by Abraham for adult depressive states. There are many ways in which an emotionally deprived child can express its frustration, anger, sense of loss and guilt. Among them are a decrease in appetite and in severe cases a total refusal of food.

Among the 35 cases of girls and women with significant hypophagia seen by me during 1937–41 only 7 approached the severity described by Gull. In all of them there was a highly disturbed emotional relation to the parent figures. Psychotherapy was often difficult in the more severe cases because the patient would not give up the pathological adaptation for a more mature one.[8, 9]

In these cases the self-starvation was but one way of expressing the inner conflict so that the total clinical picture might resemble hysterical or obsessional states, depression or even schizophrenia. The meaning of food ingestion, the gaining of weight in order to be a healthy adult who can carry responsibilities including being a childbearing mother, is the central issue.[16, 49]

In hundreds of eating disorders seen in the army I saw only 1 young male with pronounced but not fatal self-induced hypophagia.

A patient reported by Tissler had a severe generalized ego disturbance since she had not developed beyond a most primitive archaic stage. The mother remained the most important part of the patient's ego. Rose in reporting 10 cases has found that adolescent eating disorders repeat earlier infant disturbances that there are a large family of related anorexias with various conflicts at their source. It is considered however that the fundamental problem of psychological anorexia may be the same from birth that is that taking food either actually or symbolically means giving up the old and taking on new forms of psychobiological integration.[3]

It seems probable that disordered appetite may be only one manifestation of a large number of psychological conflicts. Study of the individual case will provide the material for understanding the conflict and the methods for resolving it.

THE RECIPROCAL RELATIONS BETWEEN ANOREXIA AND OBESITY

Because food ingestion and related gastrointestinal functions are among the earliest and most important in the lives of everyone, it is to be expected that these functions will suffer with later personality disorders. While we are learning to control our infantile appetites until we have acceptable food habits and table manners, we must also learn how to live with and deal with the people in our environment. If environmental circumstances encourage eating large amounts, frequently there will develop a tendency to overweight in most persons. If there is environmental pressure to resist all pleasures of the flesh, including food, we are not unlikely to find thin people who are also more ascetic in other ways. However, sometimes repression is not expressed by a relatively simple prohibition, but rather by its opposite which can be thought of as a compensatory state. This may be seen occasionally as an exaggerated kindness which cloaks concern over internal hostility, or an unnecessary punctuality or cleanliness which guards against more lax habits. In this sense hyperphagia may be a highly organized counterpart of hypophagia, serving unconscious purposes. There is a resemblance to the two phases, mania and depression, in manic-depressive disease, these two phases do not resemble each other clinically, but are closely associated dynamically. We have already mentioned the close relation between some eating disorders and the depressions. Clinically we know that infantile eating disturbances appear to be important in the history of either anorexic or obese persons, and it is not unusual to find a history of disordered eating including hypophagia in persons who are later obese, as do we find hyperphagic phases in some anorexic persons. A patient I saw illustrates several aspects of the problem. This good-looking, well-educated, conventional girl, aged twenty-four, was admitted to the hospital in an acutely disturbed state complicated by severe starvation and alcoholism of recent origin, and highly destructive behavior at home. She quieted down in the hospital but was committed to a state hospital for further treatment. Here she was assigned to work in the kitchen where she became markedly overweight. When sent home on trial visits she reverted to her former pattern of not eating, being abusive and destructive toward her mother and sister and even stealing groceries from home in order to get money for alcohol. Upon return to the hospital she regained her composure and her weight. The onset of the psychosis seemed to be related to the break in her dependence upon her older sister when the latter married. The sister had been the patient's mentor for many years, both in school and on jobs. As she advanced occupationally, the older sister helped improve the status of the patient. At the time of her marriage the older girl even managed to have the patient take over her job as private secretary to an executive. This was the setting when the patient began her regressive pattern. She could not accept her new responsibility for herself, or the threat implicitly present, to be a good helper to a male boss. Her vacillation between a state of anorexia and bulimia depended upon the external circumstances.

A case from Szurek's clinic at the Langley Porter Clinic, illustrating the

reciprocal relations between anorexia and obesity, is also unusually valuable in exhibiting treatment methods which are useful in severe cases.[6] The patient, Jean, aged twelve and one half years, was admitted to the hospital with a presenting complaint of a 45-pound weight loss from 98 to 53 pounds due to severe self imposed starvation. She had been a pretty, somewhat obese girl before the present illness. Just before the onset, the following circumstances occurred: her schoolmates were unkind in their remarks that she should diet because she was fat and unattractive; she became curious at this time about birth and conception; a friendly neighbor boy turned his attention to another girl; her father was severely beaten in a quarrel with the other girl's relatives. This latter event assumed great importance because it signalled the loss of status in both the parents' own eyes and in those of Jean. Weight loss was precipitate following this and her cadaverous condition compelled action. The usual medical and surgical methods of feeding were inadequate; the psychiatrists knew from past experience that ordinary interviews would not be sufficient so they decided upon a more active treatment program. One therapist was assigned to the patient, a second to the mother and a third to the father while all of them were supervised by Dr. Szurek.

The manifold tribulations of this team are described briefly in their report but with sufficient content to enable the reader to gain some knowledge of the methods of collaborative therapy.

The therapeutic progress of Jean during a twenty month period may be described as a process in which the girl's hostility to herself and to her parents was deflected upon her therapist. Simultaneously she obtained from him and other ward personnel some increased gratifications ("intake," "supplies") making the self directed hostility less essential and thus enabling her to eat. As the parents regained confidence and self respect they were able to give the patient more "intake" and thus encourage her to eat. The authors point out that although there was much improvement in all three, none of them solved their basic conflicts because the mother continued to be depressive and overeat, the father continued to be alcoholic and Jean returned to an obese state which needed correction. The reversal of an obese state to a cachetic one and a return to the obese is, however, of independent importance. A follow-up report in 1957 shows that she is now married, has two children, remains moderately obese, and seems to be developing a paranoid state.

THE PSYCHODYNAMICS OF HYPERPHAGIA (OBESITY)

In view of the material already presented and that present in other chapters there is no need to discuss more than a few psychological aspects of that pronounced disorder of appetite, overeating, which leads to obesity. We have frequently mentioned the symbolic satisfactions which implement the attainment of distant goals. This material can be verified by patient clinical investigation. The enlarged body may be envisioned as a fortress-like defense against a hostile world, a symbol of independence, importance and prowess, an intimidation to enemies, a symbol of a wished-for pregnancy and paradoxically a means of discouraging suitors, or, more simply

a mask for the emotions The underactivity frequently associated with *corpulence permits the* person to risk fewer stakes in the ordinary daily transactions of life, and thus helps keep anxiety low [10 11]

A *second group of eating* values centers around the immediate satisfactions and sensory pleasures of oral *incorporation* Most of us experience *more or less immediate pleasure from eating good food*, but the problem in overeating involves the interpersonal transactions which are involved [27] Many *persons at times use food as a means of* allaying tension, anxiety, guilt, frustration, anger, self-depreciation, sorrow or depression These food ingestion patterns can be altered effectively when *circumstances give* them non-food "supplies" from other sources This helps explain why obesity may be a self-limiting disorder or why it may be *amenable to ordinary*, superficial, manipulative or supportive therapies The initial success of ordinary dieting regimens become more intelligible in this light, especially if some drug is prescribed concomitantly by an enthusiastic, forceful physician This point of view also helps explain why the social clubs of obese persons, modelled upon Alcoholics Anonymous, may do much good for those who can use the companionship provided in these organizations

OTHER DISORDERS OF APPETITE

Pica —If space permitted, there are numerous other disorders of appetite which might engage our attention, as well as the disorders of related functions such as swallowing (*e g* dysphagia and globus hystericus) Perhaps the best known is the disordered appetite of some women during pregnancy, known as pica Pica is defined by DeLee as the desire for unusual things, which may include "chalk, slate, pencils or clay, salt or sand "[21] He cites the case of a woman who craved a bite of her husband's arm, and actually took it There are numerous interpretations possible in individual cases, but the basic meaning is related to the uncertainty, fear, or guilt aroused by the pregnancy and *the revival of earlier memories* Eating disorders, especially increased appetite, are common in pregnancy, apparently in reaction to frustration *at inadequate "intake ' from the* husband and family, similar to the cases described earlier Fortunately the bizarre craving for odd foods, or the unreasonable aversion to some ordinary food usually disappears after the delivery unless the patient is suffering from a major psychosis

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Chapter 5

Physiology of Hunger, Appetite and Satiety

By John R Brobeck

The obvious progress in nutrition during the past fifty years sometimes obscures the fact that one of the fundamental and most important problems of nutrition has not been solved It has not even been studied extensively It is the question "Why do animals eat?"—a question of interest to physicians because it touches on the treatment of obesity, leanness and certain metabolic diseases, and the management of feeding problems in infants and children The answer to this question should explain both overeating and failure to eat, why certain foods are preferred to others, and why particular foodstuffs are sometimes in special demand It should account for the normal cycles of appetite and satiety, and identify the factors determining the total amount of food consumed per day, the intake at any given meal, and the frequency of mealtimes or feeding periods

All of these problems appear to be related to the reactions known as hunger, appetite and satiety with which everyone is more or less familiar from personal experience Since these reactions and the names used to identify them are so widely known, we might expect the nature of the reactions and the meanings of the terms to be equally well known, but this is not the case In spite of the attempts of numerous authors to define them precisely so that they may be used in a technical sense without misunderstanding, there remains no agreement as to the meaning of any of them Much of the difficulty comes from the subjective nature of these reactions, they are sensations or psychological states, known to us *only* from our own experience This is a fatal limitation in any attempt to use the words objectively, and it makes it impossible to deal with hunger, appetite, or satiety in any satisfactory quantitative way They cannot be studied in lower animals, nor in infants Because of all of these difficulties and others, the attention of physiologists has shifted to a somewhat broader topic, the regulation of food intake, which is objective in its meaning and which refers to a variable—feeding—that can be measured The word "regulation" is used as it is in speaking of the regulation of other processes in living systems such as the respiratory minute volume, the blood pressure, heart rate, body temperature, or the concentration of water in body fluids

Within the past twenty years the nature of the regulation of feeding has become clearer, with the result that our present understanding of the subject compares favorably, for example, with knowledge of the regulation of pulmonary ventilation The two regulations appear to have many features in common In the one case, respiration the location of medullary "centers" has been established, while some of the factors affecting these centers

have been identified including the composition of the blood and reflexes from lungs and from the carotid and aortic bodies In the other case, feeding, the important "centers" appear to lie within the hypothalamus Reflexes from the digestive tract appear to be analogous to those from lungs and chemoceptors, while other reflex patterns and the composition of body fluids likewise participate in the regulation The following discussion is a review of the evidence as to the location of the central regulatory mechanisms, the identity of the factors which act upon them, and the neural basis, so far as it is known of feeding behavior

Hunger Sensation—The first to be discovered of the several components of this regulating system is the hunger mechanism, studied at length by Cannon and Washburn,[9] and by Carlson and his collaborators [10] Most physicians have had an opportunity to repeat these earlier experiments, to correlate the sensation with contractions of the empty stomach, and to study the factors such as smoking a cigarette tightening the belt drinking cold water etc which inhibit the contractions and abolish the sensation Carlson s careful account of his observations a monograph forty years old and unhappily difficult to purchase remains as one of the most important American contributions to the literature of physiology His first two chapters on the biological significance of hunger, and the review of the theories of hunger and appetite are invaluable At the time of publication of Carlson s monograph, hunger was the only physiological mechanism known to be concerned with feeding Appetite was discussed, but most of Carlson's conclusions as to its nature were based upon inferences His three excellent chapters on the nervous control of the hunger mechanism conclude with this statement 'In the afferent phase of the hunger complex the facts clearly established are the role of the vagi and the sensory vagi nuclei in the medulla, and the great importance of the thalamus * The cortical factors in hunger are unknown, and the same applies to the detailed roles of the subcortical hunger centers both in health and disease This field of the physiology of hunger is therefore mainly 'gaps and guesses It remains for the *clinical investigator* to correct the guesses and fill up the gaps as very little can be done with these problems on animals below man, at least with the methods so far available to the physiologist"

The area covered by Carlson's gaps and guesses' has proved to include the more important mechanisms of the regulation, but the filling in has been done not by clinical investigators but by laboratory scientists in experiments performed upon lower animals The interest of Cannon and Carlson was focused upon hunger as a sensation the site of the sensory receptor and the nature of the stimulus all of which can be studied best in conscious human subjects A regulation, on the other hand, can be studied in laboratory animals by measuring the food intake, or the rate and frequency of feeding The importance of both environmental and metabolic factors can be studied together with the feeding response when the composition of the diet is changed, or following operations upon selected parts of the digestive tract, the endocrine system, or the brain Investigations of these variables has revealed that the regulation of feeding includes

* Carlson did not distinguish between thalamus and hypothalamus

a variety of mechanisms reactions, and factors, of which hunger is only one component

Several authors, *e g*, Strominger,[34] Larsson,[23] and Janowitz,[18] have noted two ways in which the hunger theory is inadequate as an explanation of the regulation of feeding The first of them is the observation mentioned by Sherrington,[33] that removal of the stomach does not alter total food intake in man or experimental animals Following gastrectomy, or removal of other portions of the digestive tract, or section of vagus and splanchnic nerves, or vagotomy and section of the spinal cord, animals continue to eat a normal amount of food The animals with section of vagi and splanchnics

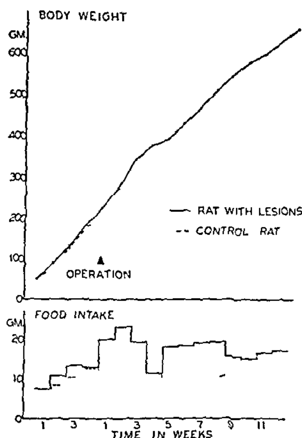


FIG 5 —Effect of appropriate hypothalamic lesions upon food intake and weight gain in the albino rat (From Brobeck *et al*, Yale J Biol Med, *15*, 831, 1943)

also show a normal increase in food intake when insulin is injected,[14] and a normal decrease when amphetamine is given [31] Sensation from the stomach and intestine, therefore, is not required for a normal regulation of quantity of food eaten The second limitation of the theory is its failure to explain variations in food intake when animals are fed different diets, or when other conditions of the experiment are altered Total food intake varies with intake per meal and frequency of feeding, it would appear that only in the latter case could variation be accounted for solely on the basis of the hunger mechanism There is no known physiological reaction which will allow hunger *per se* to determine the amount of food eaten per meal, since hunger usually disappears with the onset of feeding

Hypothalamic Control —The importance of the central nervous system in regulating food intake was discovered through the study of animals with lesions in the hypothalamus A definite hyperphagia of hypothalamic origin, mentioned briefly by Keller and his associates,[1] was more completely described by Brobeck, Tepperman and Long[6] [6] who found it to be a primary cause of hypothalamic obesity (Hetherington and Ranson)[15] This hyperphagia was also noted and described by Brooks,[7] Kennedy[2] Stevenson,[8] Van Putten[37] Mayer,[6] Anand[2] Larsson,[73] and others The abnormality may develop almost immediately following the operation when the animal may appear to be ravenous, 'attacking and 'devouring'' its food An intake of two or three times the normal food consumption, persisting at this level for weeks or even months, is not unusual The animals, whether rats, cats, dogs or monkeys, become obese to a marked degree

REGULATION OF ENERGY EXCHANGE

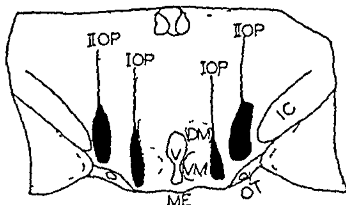


FIG 6 —Transverse section through tuberal region of hypothalamus Medical lesions (I OP) induced hyperphagia and obesity while lateral lesions (II OP) abolished feeding ME median eminence OT optic tract IC internal capsule DM dorsomedial nucleu VM ventromedial nucleus V third ventricle (From Anand and Brobeck Yale J Biol Med 24 123 1951)

Discovery of hypothalamic hyperphagia indicated that the nervous mechanisms regulating feeding have at least two distinct components or functions These are analogous to appetite and satiety if these words may be used to denote physiological mechanisms rather than subjective states The hypothalamic lesions inducing hyperphagia presumably interfere with satiety, leaving appetite mechanisms unopposed in their action, thus leading to gross overeating[3] Anand's observations however, have shown that the appetite mechanism is also represented in the hypothalamus more laterally located than the satiety mechanism[2] By placing small discrete lesions in all parts of the hypothalamus of cats and rats Anand confirmed the work of earlier authors regarding the overeating induced by medial lesions in the neighborhood of the ventromedial nuclei bilaterally But he also noted that lesions in the lateral hypothalamic area brought about a complete failure of feeding, an aphagia These latter animals did not appear to be abnormal in other respects, they were not somnolent, exhibited

no gross changes in behavior or locomotion, and maintained a normal body temperature (They were not tested in hot or cold environments.) If the operation was designed to produce both medial and lateral lesions, the animals always failed to eat, while animals becoming obese as a result of medial lesions abruptly stopped eating when lateral lesions were created.

Anand's results have been confirmed by other investigators, while the importance of the hypothalamus has also been supported by authors using other methods. Delgado and Anand implanted electrodes in the hypothalamus of cats, using a technique which permitted the stimulation of the brain under waking conditions.[19] By stimulating the brain for two hours daily, they induced an increased total food intake which persisted throughout the period. They did not observe feeding during the stimulation even though food was presented then; the hyperphagia took place in the period when no stimulus was applied. Larsson, on the other hand, using either electrical stimulation or the injection of hypertonic solutions into the hypothalamus of unanesthetized goats, noted eating during the period of stimulation.[3] An earlier paper by Brugger, reviewing the results of stimulation experiments performed by Hess upon unanesthetized cats, also mentions feeding and related behavior, such as licking and chewing.[8] Brugger's report differs somewhat from the others as to the exact location of the active regions, and the regions which he found active have not responded in a similar manner in the experiments of other investigators.

Using a somewhat different method of stimulation, Olds has also obtained data relating the hypothalamus to feeding behavior.[79] He used implanted electrodes under conditions where the stimulus was turned on by the rat when it touched a control switch within its cage. With the electrodes in certain locations, rats stimulated themselves at rates of up to 5000 times per hour. At certain intensities of current there were correlations between the rate of stimulation and whether the rat had been fasted or fed. In some instances the animal stimulated itself and created an increase of food intake. The author noted that his data suggest a "sharp localization of the hunger reward center in the hypothalamus and a very compact relation between it and the other drive-reward centers in the hypothalamus . . . ." (p. 321)

There is abundant evidence, therefore, that the hypothalamus contains a mechanism capable of initiating feeding, in addition to a mechanism which normally prevents overfeeding. Destruction of the former leads to aphagia, of the latter to hyperphagia. Even relatively small lesions of the hypothalamus will cause striking changes in feeding when placed bilaterally in the proper location. In rats, the destruction of a sphere having a diameter of less than 1 millimeter in the lateral hypothalamic areas of both sides of the brain is followed by death from starvation. No comparable change follows operations upon the stomach, duodenum, or their nerve supply, whether sensory or motor. This is the basis for the conclusion that the nervous system rather than the digestive tract is the regulator of food intake. Several names have been given to the hypothalamic mechanism, including the term "feeding center," used by Anand and Brobeck. Jolliffe has suggested the name "appestat," because the function of the hypothalamus in regulating feeding is thought to resemble the action of a thermostat.[0]

Basis of Regulation.—There now appears to be a general agreement regarding the importance of the hypothalamus and it is often assumed that the hypothalamus contains sensitive cells or receptor elements which respond to some change when food is eaten or when food is needed. It should be noted, however, that the presence of these sensitive cells within the hypothalamus is known only by inference from experiments such as those of Larsson[3] (see above), of Verney[38] or of Andersson[3] who studied osmotic pressure receptors in the hypothalamus or those of Barbour[4] or Magoun *et al.*,[24] who studied temperature reception. The hypothalamus may well contain such receptor elements for feeding but their presence is not established. Furthermore it seems almost certain that feeding is not controlled by way of any one receptor system in response to some one change within the body.

The most controversial topic in this field of study is the nature of what is being regulated. Is the important factor the volume of the food, its weight, its caloric value, the carbohydrate it contains or its protein concentration? Is filling of the stomach the critical reaction or is it some change in body fluids caused by absorption of the products of digestion? Is there some change in the rate of a key metabolic reaction when food is eaten, with an opposing change when food is needed? All of these and other factors have been proposed and every one is supported by a certain amount of reasonable but not decisive evidence.[18] If there is truth as there appears to be in all of the various proposals, then there must be many bases for the regulation and a multiple factor theory is necessary to explain all of the facts (Janowitz and Grossman[19]). These factors include the hunger mechanism and other sensations from the stomach. Thus filling the stomach with food through a gastrostomy tends to diminish the quantity of food a dog will eat spontaneously.[3] Similarly, allowing a dog to eat while the food leaves the body through an esophageal fistula reduces the amount of food taken at a subsequent meal.[19] These results emphasize the importance of the afferent impulses from the digestive tract whether from mouth, pharynx and upper esophagus or from the stomach and possibly the small intestine[17] and further indicate the presence of receptor elements in the gut.

Additional factors believed to be important are the caloric value of the diet (Cowgill,[11] Adolph,[1] Strominger[35]), the state of hydration of the body (dehydrated animals fail to eat), the conditions of temperature regulation and the specific dynamic action of the food[34] (animals do not eat when they cannot dispose of this extra heat) and the availability of glucose as a source of energy in the central nervous system. This last factor has been emphasized by Mayer and his associates.[6] The possibility that the composition of the diet may be important is suggested by the observation that animals with hypothalamic lesions as well as mice with the obesity induced by gold thioglucose[13, 39] gain weight most slowly on a high protein diet and most rapidly on a high fat diet. Moreover, in normal adult animals all authors seem agreed that high protein diets have greatest satiety value. This appears to justify the use of high protein diets in treating obesity in human patients.

Feeding Reflexes.—The idea that many factors are important in this regulation gains further support from some of the basic principles of

neurophysiology, which are pertinent here if the regulation is a function of the brain In all, or nearly all, of the functions of the central nervous system, the unit of response is a reflex, which may be either facilitated or inhibited by nerve impulses derived from other reflexes or from other portions of the nervous system Metabolic, hormonal, and chemical factors also modify the intensity of reflex actions The neural complex for the regulation of feeding is almost certainly analogous to the mechanisms which regulate circulation respiration, body temperature, and many other

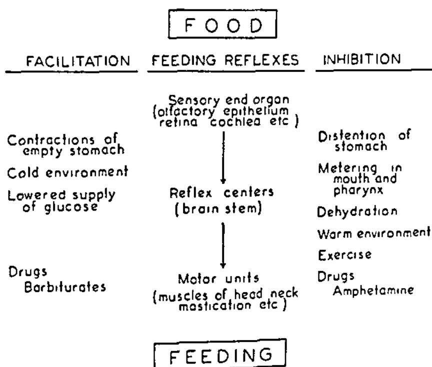


FIG 7 —Diagram of basic reflex pathways concerned with feeding, with factors believed to facilitate and to inhibit these reflexes

variables All of these are regulated through certain patterns of reflexes, plus in some instances, nerve impulses which seem to arise spontaneously within limited regions of the brain stem The important reflexes in feeding probably include those which can be observed in decerebrate animals (chewing and swallowing reflexes, reflex salivation, etc [27]), plus reflexes of the type seen in newborn infants—"rooting," grasping with the lips, sucking, and swallowing Each animal species may have reflexes peculiar to the species, but it appears that among mammalian forms certain individual reflexes may be common to all In addition, chemical and physical changes in the composition of body fluids are probably important just as they are in the regulation of respiration, while metabolic factors, too, may have their respective roles

The function of the hypothalamus and of higher levels of the nervous system appears to be the selective facilitation or inhibition of this reflex activity When feeding is the only variable in the experiment, where an animal is fed *ad libitum* and is not disturbed in any way, the integration of

factors and responses necessary for regulation of feeding may be accomplished at the hypothalamic level. But when other variables are introduced, such as sensation, emotion, volition, choices between foods or between food and other objects, the cerebral cortex probably contributes to the regulation. Both the cerebral cortex and the hypothalamus, however, eventually must act on feeding through either facilitation or inhibition of the basic reflexes (or by increasing or decreasing the animal's locomotor activity—see below). As an illustration of reflex feeding activity as modified by the hypothalamus, consider the feeding behavior of an animal living continuously in the presence of food, as is the case with many farm animals and most laboratory animals. In spite of the constant stimulus of food nearby, most animals will not eat constantly but will eat periodic "meals." Reflexes which might be initiated continuously by the sight or odor of food or by contact with it, are not invariably completed and for prolonged intervals the animal behaves as though it were unaware of the food. An animal with lesions in the lateral hypothalamus shows the same type of behavior, a complete lack of awareness of the presence of food plus an active resistance to any attempt to induce it to eat. The lateral hypothalamus, therefore, appears to be a facilitatory mechanism whose activity is necessary for the completion of feeding reflexes. The medial hypothalamus, on the other hand, appears to be an inhibitory mechanism, acting upon the lateral one or upon the reflex centers directly. Appetite in an objective sense is the result of activity of the lateral mechanism, satiety, of the medial.

Activity Precedes Feeding.—Like facilitation of feeding reflexes, the increased locomotor activity of a hungry animal appears to originate in the hypothalamus. Locomotor activity is diminished in animals with certain lesions of the hypothalamus[16] (although this change is not necessarily correlated with a corresponding change in food intake). In normal animals, the facilitation of activity and of feeding reflexes function together to bring the animal into the presence of food and to lead to its investigation and ingestion. The role of the cerebral cortex in these reactions is largely a matter of speculation at the present time. A number of studies suggest the presence of cortical factors but their nature is obscure, with the exception of the discovery of Pribram that following ablation of certain cortical areas, monkeys and baboons appear to be unable to recognize inedible objects.[30] They will eat any object small enough to be eaten including assorted hardware and lighted matches. When only food is presented, however, they eat a normal quantity. These observations and many others can easily be included in the scheme of regulation given here as extra sources of facilitation or inhibition of feeding reflexes, possibly acting in turn, through facilitation or inhibition of the hypothalamic mechanisms.

Summary.—Regulation of feeding is believed to be accomplished through hypothalamic mechanisms which control (*a*) the excitability of the basic reflex arcs composing feeding reflexes and (*b*) the amount of the animal's locomotor activity. The mechanisms within the hypothalamus appear to possess reciprocal action, either increasing locomotion and facilitating the feeding reflexes or decreasing locomotion and inhibiting the reflexes. The central mechanisms respond to a variety of changes in the animal and its environment, including feeding behavior *per se*, the presence or absence of

material in the stomach and intestine, the state of bodily hydration, the conditions of temperature regulation, and certain metabolic reactions related to the intermediary metabolism of the nervous system Regulation of locomotor activity thus governs the possibility that food will be encountered, while regulation of feeding reflexes determines whether or not an object will be investigated, taken within the mouth, chewed and swallowed

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Chapter 6

Digestion, Absorption and Metabolism of Protein

By Ernest Geiger

INTRODUCTION

Proteins are indispensable constituents of the living protoplasm and participate as such in all vital processes. The specific structure of the various body proteins imparts particular properties which are determinants of growth, neuromuscular and mental functions, of enzymatic and hormonal processes, immunological phenomena, physicochemical properties of tissue fluids, of many other organ functions and indirectly of reproduction and heredity.

The initial production and continuing maintenance of these body proteins * evidently a necessary condition of all life processes depends on the dietary intake of its building stones, primarily of some specific amino acids, but also of substances from which other amino acids may be formed in the body itself. The *quantity* of the building stones of the body proteins present in the diet closely parallels its nitrogen content. It is therefore customary to express the "protein value" of food on the basis of the amount of organic nitrogen present. However, such a method in spite of its expediency, does not take into consideration the fact that the nitrogen containing substances of our diet serve in several roles in addition to the synthesis of body proteins.

Besides the proteins the human body contains a large variety of other nitrogenous organic substances. Such substances are the purines and pyrimidine bases, constituents of nucleo-proteins, creatine one of the key substances in energy transfer, choline and many other nitrogen containing compounds of more or less clearly recognized biological significance. Many of these nitrogenous substances, for instance the essential amino acids and some vitamins, must be obtained ready-made from the food but others can be formed within the body from other sources. Ultimately, however, the formation of all these tissue constituents during growth and also for replacement during adult life requires the dietary supply of nitrogen containing substances. The biosynthesis of many amino acids, of creatine, of choline, and of other compounds has long been postulated but the pathways of such syntheses were only recently elucidated by following the metabolic fate of compounds tagged with isotopes.[2] We have learned by application of such methods that the proteins present in the food are used not only for

* The human body contains 18.62 per cent protein or, calculated on a water free basis, about 42 per cent of the total solids are composed of proteins. This analysis is only a crude approximation because the factor (N × 6.25) used for calculation does not take into consideration the nitrogen content of some other nitrogenous substances.[1]

building of new tissue proteins or for replacing the proteins which were destroyed by the ominous "wear and tear," but also that one fraction of the dietary proteins or amino acids is utilized for the biosynthesis of other non-protein nitrogen containing compounds We learned furthermore that dietary nitrogen supplied not only as organic compounds but even in the form of inorganic ammonium salts can be utilized in the synthesis of several amino acids, and therefore, some synthetic diets which did not support growth could be effectively supplemented by the addition of in organic nitrogen sources such as ammonium salts[3] All this indicates that the present concept of "proteins in nutrition" is probably too narrow and that in the future evaluation of the nutritive value of diets not only the amino acid content, but also the presence and distribution of other nitrogen containing compounds will have to be considered

Recent discoveries in the field of intermediary metabolism have broken down many boundaries which separated protein, *i e*, amino acid metabolism, from other fractions of the general metabolism Nutritional research has kept pace well with these developments, but there is still some tendency to depend in human, and especially in therapeutic nutrition, on unsatisfactory methods, a tendency to apply confusing definitions and to adhere to obsolete nomenclature These tendencies are illustrated by such practices as determining the "protein intake" indiscriminately by multiplying the nitrogen content of the diet by 6 25, or defining the protein requirement without specifying the total diet composition or the condition of the person to be fed Another misleading habit is identification of decreased urinary nitrogen excretion with "protein anabolism"

The nature of human nutritional research makes it mandatory to rely in our further discussions of the physiology of protein nutrition primarily on data collected in connection with normal mixed food intake Without any prejudice as to whether our present Western dietary could be improved by changing the quantity or quality of protein intake, we must accept the fact that the self-selected mixed diets have been conducive to health and good development and, along with other hygienic factors, have contributed to an unprecedented long-life-expectancy and to healthy old age Data collected by nutrition surveys are therefore very valuable in studying the role of proteins in human nutrition Certain problems, for instance the quantitative amino acid requirements have been studied by feeding more or less synthetic diets to man Finally, there are many problems which have not yet been investigated in humans, and in discussion of these questions we shall have to rely on analogies based on animal experiments

SOURCES AND UTILIZATION OF DIETARY PROTEINS

The dietary protein intake derives from animal and vegetable sources and accordingly the protein content of the different food substances varies considerably as demonstrated in Table 6 Calculations based on the average pre-war dietaries consumed in the Western civilizations show that protein accounted on the average for 14 per cent of the total calories and only in exceptional cases fell below 10 per cent[4] Further calculations proved that

the protein in an average food intake of 2,500 calories is about 94 grams per day. Table 9 also indicates that the protein content of meals prepared from natural food sources has a definite upper limit. Recently therapeutic diets have been recommended which contain higher quantities of protein than our normal mixed foods. In order to achieve this without increasing the total caloric intake or without consuming monotonous diets composed only of high protein foods, the mixed diets are enriched by addition of certain special purpose foods like spray dried egg white, skim milk powder, or any of the commercially available protein concentrates obtained from natural foods such as casein, soy protein or defatted dried lean meat.

TABLE 9.—PROTEIN CONTENT OF COMMON FOODS

Edible Food Substances	*Calories per 100 Grams*	*Protein per 100 Grams*	*Protein* Calories per 100 Grams Food*	*Protein Calories in per cent of Total Calories*
Pork meat, medium fat (cooked)	457	14.9	63.6	13.9
Beef meat, medium fat (cooked)	273	17.5	74.7	27.4
Chicken meat (total edible)	302	18.0	76.9	25.5
Fish fillet (unspecified)	132	18.8	80.1	60.7
Canned tuna (low fat)	128	28.3	120.6	95.0
Canned tuna in oil	217	27.7	118.0	54.4
Pacific sardines (canned in tomatoes)	216	17.8	76.0	35.2
Salmon, canned	173	20.2	86.3	49.9
Eggs, fresh	144	11	48.0	33.3
Eggs, dehydrated	605	47	204.9	33.9
Milk, whole	68	3.5	14.9	22.0
Skim milk, dry	360	36	153.7	42.7
Cheese, hard	341	34	145.2	42.6
Whey cheese, soft	106	14	59.8	56.4
Rice	360	6.7	25.6	7.1
Corn	356	9.3	35.5	10.0
Wheat flour (medium extraction)	350	11.7	45.6	13.0
Potatoes	70	1.7	4.65	6.7
Soybean grits	261	46	159.6	61.2
Beans, peas, dry	345	22.2	77.0	22.3
Cabbage, fresh	11	1.1	2.68	24.4
Fresh fruits (group figure)	46	0.5	1.68	3.65

* Calculated by using The Specific Physiological Energy Factors.[4]

In contrast to the Western diet, the food in some underdeveloped countries of the Orient or Africa, where primarily starches, roots, vegetables and fruits are consumed, usually contains much lower quantities of proteins that, moreover, are of unsatisfactory quality.[5] The deleterious effect of such protein deficient diets has been amply documented in some of the older and many of the more recent treatises.[6]

Digestion of Proteins.—Our regular food consists of more or less denatured animal or vegetable tissue which contains the protein as a constituent of its protoplasm. One part of the protein is conjugated to other substances and the rest is usually thoroughly mixed with or closely surrounded by other substances, mainly carbohydrates and lipids. The pres-

ence of free protein is very rare in nature, an outstanding exceptional example is found in egg white. Likewise the natural or prepared foods contain free amino acids as such only in negligible quantities. The dietary proteins are macromolecular substances which are not absorbed to any considerable degree across the intestinal barrier and cannot be utilized by the body even when introduced parenterally. This means that as a rule *only* the amino acids, the smallest units of dietary proteins, can be utilized by the body as building stones for tissue protein synthesis. It has been shown that even small protein fragments such as peptides containing only few amino acids cannot be utilized by the tissues *in most instances* and are usually eliminated unaltered in the urine.

TABLE 10.—PROTEOLYTIC ENZYMES

Enzyme	*Produced in*	*Splits preferentially peptide linkages*	pH *optimum*
A. PROTEINASES: Attack peptide linkages in the interior of a peptide chain			
Pepsin	Stomach	In which phenylalanine or tyrosine provides amino group	1.8–2.0
Trypsin	Pancreas	In which arginine or lysine provides carboxyl group	8–9
Chymotrypsin	Pancreas	In which carboxyl group provided by tyrosine, phenylalanine, tryptophan or methionine	8–9
Cathepsin A	Tissue cells	Similar to pepsin	
Cathepsin B*		Similar to trypsin	3.5–6
Cathepsin C*		Similar to chymotrypsin	3.5–6
B. PEPTIDASES: Attack peptide linkages formed by terminal amino acids			
Carboxypeptidase	Pancreas	Next to terminal carboxyl group	7.2
Aminopeptidase	Intestines	Next to terminal amino group	7.4
Prolinase	Intestinal	Formed by proline	6.0
Prolidase	cells		

* Presence of reducing agents such as cysteine necessary for maximal activity.

In contrast to these earlier results P. R. Cannon, L. E. Frazier and R. H. Hughes (Science, *119*, 578, 1954) reported recently "that at least some simple peptides can be utilized parenterally in tissue protein synthesis."

Proteins are composed of a variety of the different α-amino acids. These are compounds which are characterized by the presence of a terminal carboxyl and of an amino group in α-position. In the protein molecule the amino acids are connected by *peptide linkages* which are formed between the carboxyl and amino group of two adjacent amino acids. The digestion of food proteins to amino acids requires, besides the enzymatic cleavage of such linkages, also the mechanical action of the digestive organs. In many cases, as a preliminary to protein cleavage, the carbohydrate or fat coating has to be broken down by these processes in order to expose the protein particles to the lytic action of gastrointestinal enzymes. The breakdown into the component amino acids occurs in the stomach and in the upper part of the intestinal tract. The proteins are split there into smaller fragments by the "proteinases" such as pepsin, trypsin, chymo-

trypsin and the resulting smaller peptides are further digested by different "peptidases" Recent studies on the specificity of the gastro intestinal enzymes, as indicated in Table 7, have changed our concepts of protein digestion The old view, according to which large molecules are attacked first by pepsin and are consequently broken down to fragments of smaller size, was based on the assumption that the peptide linkages formed between the amino and carboxyl groups of adjacent amino acids are equivalent It was assumed that these linkages by which the amino acids are connected within the protein molecule can be attacked by any proteolytic enzyme and that the selective action of pepsin trypsin or other enzymes is determined by the size, shape configuration and other physico-chemical properties of the protein molecule However recent investigations proved that, although the peptide bonds between the different amino acids seem to be identical, their resistance to cleavage by proteolytic enzymes is different It depends on the chemical nature of the amino acids which participate in the formation of a particular peptide bond[7] (see Table 10) The polypeptide chains, the components of larger protein particles, usually have a free amino group at one end and on the other a free carboxyl-group, and free polar groups seem to be necessary for the action of many proteolytic enzymes Only proline, which contains an imino instead of an amino group, forms peptides lacking the terminal amino group The high resistance of proline containing peptides to enzymatic cleavage was recognized at the beginning of this century but specific enzymes which can split such peptides have only recently been studied and isolated [8]

In some cases, however, the terminal amino and carboxyl groups also participate in peptide formation resulting in ring closure Such polypeptide links are particularly resistant to enzymatic cleavage This may explain why some antibiotics such as gramicidin or some toxins are not digested not broken down to their constituent amino acids Some of them such as phalloidin are instead absorbed unaltered, producing toxic effects within the tissues

The *p*H of the surrounding medium affects the ionization of the terminal amino or carboxyl groups and this seems to be the mechanism by which the *p*H of the medium influences the digestibility by enzymes The normally high acidity in the stomach provides the *p*H optimum for cleavage by pepsin and the low hydrogen ion concentration in the intestines produces conditions favorable for digestion by pancreatic and intestinal enzymes

More recent investigations indicate that besides the classical peptide bonds some additional linkages are also involved in the shaping and stabilization of protein molecules The β and γ carboxyls of glutamic and aspartic acid, the non α amino groups of arginine or lysine the SH groups of the sulphur containing amino acids and hydrogen bonds form such additional linkages within the polypeptide chain or serve as cross-linkages to connect such adjacent chains [9] All of these linkages evidently may affect enzymatic cleavage According to recent investigations, the gastro-intestinal enzymes attack not only peptides but also some of these additional linkages present in the protein *e g*, it has been demonstrated that pepsin depolymerizes protein by splitting certain cross-linkages

Some of the non-peptide linkages are split by denaturation of the protein, therefore heating or even denaturation by the high acidity in the stomach often facilitates enzymatic digestion A well-accepted example of this effect is that of heat which, by *destroying such additional linkages*, uncoils the folded proteins and exposes thus a larger surface to enzymatic attack It should, however, be pointed out here that excessive or prolonged heating during food preparation may sometimes form some extra linkages and thus decrease the digestibility of proteins It was found, for instance, that the toasting of cereal products decreases the physiological availability of lysine, tryptophan and other amino acids [10]

The presence of bonds which cannot be split or can be cleaved only with difficulty by the gastro-intestinal enzymes is of the highest nutritional importance This is usually the reason why in actual feeding tests proteins do not always show the biological values predicted on the basis of the chemically determined amino acid content after acid or alkali hydrolysis Heating with strong acids or bases evidently can liberate amino acids from complexes which withstand the action of the digestive enzymes [11]

The sequence of the several phases of protein digestion, such as the peptic action and the preparation of the masticated food in the stomach, the emptying of the stomach contents into the duodenum, the slow propulsion along the small intestine, and the successive action of the different proteases and peptidases in the stomach and intestine, suggests that the process of protein digestion is a well-integrated "whole" Some of the phases and the physiological significance of these processes are only fragmentarily understood * One of the most important problems seems to be whether the role of proteases and peptidases is solely to split dietary proteins to amino acids for absorption or whether, in addition, these enzymes fulfill some other physiological functions It is evident that the products of pepsin, trypsin, and erepsine digestion are different because of the selective cleavage of certain well defined peptide linkages It seems intriguing therefore, to consider whether these products must fulfill some specific tasks before their terminal breakdown to absorbable amino acids Their presence may regulate gastro-intestinal motility and their lack or overproduction may be responsible for some of the vaguely defined symptoms of gastro-intestinal indisposition

Pepsin, for instance, does not seem to be absolutely essential for the final digestion of proteins Its absence need not upset intestinal digestion, as found in *achylia gastrica* where the over-all utilization of protein for maintenance of nitrogen equilibrium is not gravely disturbed Many clinical symptoms observed in this disease suggest, however, that the products of peptic digestion may have their own specific physiological action and there are some indications that the production of Castles intrinsic factor may be connected with the products of peptic digestion [13]

Intestinal Absorption of Amino Acids —The amino acids liberated from the food proteins by enzymatic processes within the intestinal tract are transferred to the tissues by means *of intestinal absorption* Occasionally some larger fragments like polypeptides or even proteins may also be ab-

* The recently demonstrated activating effect of some bile acids on protein digestion *in vitro* raises the question of how the bile production affects protein digestion *in vivo* [12]

sorbed These larger fragments, as mentioned earlier, cannot be utilized for protein synthesis[14] however, they apparently can and do lead to immunological sensitizations and thus may be responsible for the development of allergic phenomena * For the most part, amino acids are absorbed from the upper part of the small intestine, but according to recent studies, other segments of the intestinal tract may participate in amino acid transfer Using S^{35} labeled proteins, it was possible to show that 11 per cent of the material was taken up by the stomach wall, 60 per cent by the small intestine and 28 per cent by the colon [15] These data suggest that both the stomach and the colon may be involved in amino acid absorption however, all attempts to improve nitrogen equilibrium by means of rectal infusions of amino acids have thus far proven unsuccessful

The exact mechanism involved in the absorption of amino acids is unclear The old view that amino acids pass through the intestinal wall by simple diffusion now seems to be untenable, in view of the complexity of the factors which may alter absorption rates It has been shown that the optical isomers of amino acids are absorbed at different rates [16] in spite of the fact that the diffusion constants predicted from the identical size and shapes of the enantiomorphs should be identical The rapid and high accumulation of labeled compounds in the mucosa cells soon after feeding isotope labeled proteins is further evidence for an active uptake of these compounds by the cells and subsequent transfer to the circulation [17] Furthermore, recent investigations show that the *in vivo* absorption of certain amino acids may be specifically inhibited by the presence of some other amino acids For example the presence of l tryptophan decreases the rate of intestinal absorption of histidine in the rat, but the rate of absorption of tryptophan seems to be unaffected by the simultaneous presence of histidine [18] In similar experiments on dogs, leucine was shown to depress the intestinal absorption of both phenylalanine and isoleucine [19] These observations support the idea of a competition between amino acids for the selective, specific processes responsible for intestinal absorption An uptake of L-amino acids, but not of the D-isomer by the rat intestine against a concentration gradient not explainable by the Donnan theory has been recently established as a further evidence for active transport [20] In general it would seem that the absorption of amino acids is an active function of the intestinal wall, although nothing concrete is yet known about the mechanism involved

Such an active absorption is likewise suggested by clinical observations Thus it was shown that when the functional characteristics of the intestinal wall are altered *e g*, in sprue or ulcerative colitis, intestinal absorption of amino acids is generally impaired [1] It has frequently been observed that after resection of large parts of the small bowel there is a profound disturbance in the patient s capacity to absorb amino acids but some five to six months after surgery the characteristics of the remaining bowel are so altered as to restore almost completely the total capacity for amino acid absorption Thus there would seem to be a functional adaptation of the intestinal mucosa

* In contradistinction to this almost generally accepted view some authors have suggested recently that peptides are normal products of intestinal absorption and that they rather than amino acids represent the normal currency of protein metabolism [14a]

gery Actual feeding experiments have proven, however, that even in extreme starvation proteins can still be digested as long as food can be swallowed It is only in the final stages of starvation that digestion is inhibited and the experiences in the western Netherlands indicated that there is no treatment available which would resuscitate such cases [6] It was also observed that protein digests were soon rejected and vomited by the patients, and still another disadvantage was the relatively large quantity of liquid which had to be consumed along with the amino acids When glucose was mixed with the protein hydrolysates, they were somewhat better tolerated, but, as a matter of fact undigested skim milk-glucose mixtures were preferred by the patients who maintained their weight more effectively The therapeutic use of protein hydrolysate in malnourished South African children provided equally disappointing results (Gillman, *cf* ref 6[b], p 147)

The use of protein hydrolysates was particularly recommended in cases of gastro-intestinal diseases It has been shown, however, that protein digestion and amino acid absorption in diseases like peptic ulcer, or ulcerative colitis, or regional enteritis are nearly normal and the use of hydrolyzed protein in such conditions seems to be unnecessary [7] All these experiments prove that the practical value of "oral" amino acid preparations have been seriously overemphasized These preparations are most valuable dietary sources of nitrogen for short term feeding in those cases where protein digestion is grossly disturbed or in cases of certain food allergies, but, because of their relatively higher cost, their low palatability, and their possible noxious effects cited above, they do not seem to be generally a practical source of nitrogen *The practice of giving a fraction of the daily nitrogen requirement in the form of amino acid drinks or tablets may have its psychological value but is obviously of no particular nutritional importance*

ESSENTIAL AND NONESSENTIAL AMINO ACIDS

Some of the amino acids required for protein synthesis in growth, repair and maintenance, must be supplied by the food but others may be produced by the body itself The amino acids which have to be supplied with the food are the so called "essentials" [8] It should be emphasized, however, that they are not more important in metabolism or growth than the others, the so-called "nonessentials" This distinction implies only a necessity for supply of the "essentials' from external sources The amino acids which are essential *for man* are listed in Table 11 which shows also that the average American diet supplies satisfactory quantities of these building stones The daily amino acid requirement of women seems to be somewhat lower than of men, however no striking differences have been found [8a] Most of the published values were established by N-balance experiments We have to keep in mind that the requirements for maintenance of N-balance for growth reproduction, lactation *etc* seem to be different [8b] If any of the essentials is missing from the diet, or is present in inadequate quantities then the dietary protein cannot be used for growth or maintenance even though the other amino acids be present in superabundant

quantities. The nonessentials which are missing from the diet can be produced in the body from other sources. Their carbon skeletons derive from intermediary products of carbohydrate and fat metabolism to which the amino group is transferred by the mechanism of transamination.[9] The biogenesis of nonessential amino acids was proved by feeding C^{14} labeled sugar or acetic acid or by injecting $C^{14}O$. The C^{14} derived necessarily from the fed sugar or fatty acid or CO_2 was incorporated into the nonessential amino acids of the milk and body proteins and the liver proteins regenerated after partial hepatectomy.[30] This proves that in building the carbon skeleton of the nonessentials, sugar or fatty acid or CO_2 was used as a precursor.

TABLE 11.—ESSENTIAL AND NONESSENTIAL AMINO ACIDS IN HUMAN NUTRITION

	Essential Amino Acids			
	*Minimum daily Requirement**	*Recommended daily intake**	*Daily intake with self selected diets***	*Nonessential amino acids*
L-tryptophan	0.25 gm	0.5 gm	0.92 gm	Glycine
L-phenylalanine	1.10	2.2	3.66	Alanine
L-lysine	0.80	1.6	6.35	Serine
L-threonine	0.50	1.0	2.86	Cystine
L-valine	0.80	1.6	4.61	Tyrosine
L-methionine	1.10	2.2	1.89	Aspartic Acid
L-leucine	1.10	2.2	6.00	Glutamic Acid
L-isoleucine	0.70	1.4	4.62	Proline
				Hydroxyproline
				Citrulline
				Histidine
				Arginine

* Rose's values are calculated for normal *males*.

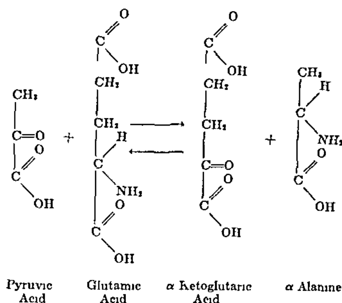
** These values were computed from data on self selected diets of *women* (Z.W. and C.W. in Table 5 of the paper of Futrell *et al.*).[139] In evaluation of these data the phenylalanine sparing action of tyrosine and the methionine sparing action of cystine have to be considered.

The essential amino acids, in contrast, did not contain any C^{14}, indicating that no new formation of these amino acids from labeled precursors had occurred. Thus the main difference between essentials and nonessentials is that the carbon skeleton of the essential amino acids cannot be formed in the animal body. The precursor of the nonessential amino acids formed in intermediary metabolism is usually the keto-analog, *e.g.*, pyruvic acid serves as precursor for alanine; an amino group is then attached to this acid. The amino group derives either from another amino acid or from the ammonia of dietary amino compounds[31] (Table 12). The transfer of the amino group from one amino acid to another is accomplished by action of the enzyme "transaminase," which is activated by the coenzyme pyridoxal phosphate. In the preparatory uptake of inorganic ammonia for the purpose of transamination, glutamic and aspartic acid seems to be the key substances.

It was demonstrated, after feeding N^{15} labeled ammonium compounds, that the essential amino acids as well as the nonessentials show uptake of

N^{15} These experiments prove the important fact that most of the essential amino acids participate also in the transamination reaction [32] As further confirmation of these results, it has been shown in rat experiments that the hydroxy- or keto-analogs of the essential amino acids, with the exception of those corresponding to lysine and threonine, could actually be used for replacement of the corresponding amino acids

TABLE 12 —TRANSAMINATION OF PYRUVIC ACID TO α ALANINE



According to these results, the amino acids participating in protein synthesis may be divided into three groups *In the first group belong lysine* and threonine which have to be supplied in "ready made" form To the second group belong the other essentials which can be supplied either in the form of amino acids or in the form of their hydroxy- or keto-analogs which can be then converted to amino acids by transamination And, finally, the nonessential amino acids which can be wholly formed from nonspecific precursors in the intermediary metabolism

The dividing line between these groups of amino acids, however, is not sharp Arginine, for example, which is a *nonessential for the adult*, cannot be formed with the necessary speed in infants, therefore, its dietary supply may be regarded as essential in early life [33] Tyrosine, furthermore, does *not show any* C^{14} *uptake after feeding of tagged* sugar or acetic acid in spite of being a nonessential amino acid The reason for this is that tyrosine is not newly formed in the body but derives from phenylalanine which is an essential amino acid Tyrosine is nonessential only because it can be formed from phenylalanine, and quantitative determinations actually show that about 50 per cent of the phenylalanine *requirement can be provided* by tyrosine In the biological evaluation of amino acid mixtures or proteins it must always be remembered that a food may be satisfactory as an amino acid source *even when it does* not contain the necessary amounts of phenylalanine as established by the determinations of Rose, provided

that enough tyrosine is present The same line of reasoning applies in the evaluation of the methionine content of proteins Cystine present in the diet may substitute for about 30 per cent of the methionine requirement, indicating that a fraction of methionine is transformed to cystine

For efficient protein synthesis, both the essential and nonessential amino acids must be available simultaneously and in sufficient quantities Although the organism does not depend on dietary intake of the nonessentials it is evident that when their dietary supply is low they must be produced in the intermediary metabolism and be provided as free amino acids in ample quantities in order to secure the optimal utilization of the essential amino acids Protein synthesis, therefore, is not limited only by the supply of essential amino acids but also by the speed and efficiency with which the so called nonessentials are made available This phenomenon is well demonstrated by experiments in which the feeding of a mixture of essential and nonessential amino acids was more effective than the feeding of the essentials only The rapid availability of the nonessential amino acids depends on the proper function of the conversion mechanisms and it seems probable that some of the disturbances of protein formation for instance in liver disease, may be the consequence of a failure in the formation of some nonessentials

THE BIOLOGICAL VALUE OF FOOD PROTEINS

The proteins provided by different food substances are not nutritionally equivalent In the past the *biological value* of a protein was determined by time and money consuming feeding experiments in which either growth promotion or repletion after protein depletion or the maintenance of nitrogen equilibrium was measured With the recent development of relatively simple methods for quantitative determination of amino acids in protein hydrolysates, e g the microbiological, enzymatic, and chromatographic methods a "chemical scoring" of proteins has been attempted This scoring is based on the assumption that the nutritive value of proteins depends entirely on their amino acid composition i e that proteins are as good as their content of essential amino acids

The F A O recently established a provisional pattern of essential amino acids[6, a] It is assumed that this "desirable" pattern provides the human amino acid requirements in optimal proportions This amino acid pattern contains per 1 gram of total nitrogen

Isoleucine	270 mg
Leucine	306
Lysine	270
Phenylalanine	180
Tyrosine	180
Sulfur-containing	
Total	270
Methionine	144
Threonine	180
Tryptophan	90
Valine	270

The nutritional value of any dietary protein can be "scored" by comparison of its amino acid content with the "desirable" pattern

The essential amino acid content of the common foods has been recently compiled by Orr and Watt[35a] This report represents a fairly good guide for designing nutritionally satisfactory meals containing proteins of different origin and chemical score

The chemical evaluation of protein is generally in quite good agreement with the values obtained by the more complicated biological methods[35] In many cases, however, the actual biological value was found to be lower than predicted on the basis of the amino acid composition The reason for this discrepancy is that not all of the amino acids present in food are necessarily physiologically available The utilization of amino acids depends primarily on the nature of the linkages by which they are connected within the protein molecule If these linkages are resistant to the highly specific digestive enzymes, the amino acids involved are not liberated and may be lost with the feces or be destroyed by the intestinal flora Such enzyme resistant linkages may be pre-formed in the protein, but they are often artifacts which are produced by protracted heating or storage of proteins, particularly in the presence of carbohydrates Thus the recent trend to evaluate proteins according to their essential amino acid content has its limitations and fallacies * A further complication in evaluation arises from the circumstance that we do not yet know how the relative concentrations of the essential amino acids and the presence of the different nonessentials influence the utilization of the amino acid groups present in the protein There is no safe way at present to establish the nutritive value of proteins otherwise than by feeding tests The chemical scoring can be used only in a negative sense, *i e*, those proteins which do not contain some of the eight essential amino acids in proper quantities cannot be utilized as such for protein synthesis in the body

The scoring of different foods according to the biological value of their proteins is of high theoretical and practical importance It has led to developing new patterns in human and animal nutrition and explains many forms of malnutrition in different parts of the world It also shows the importance of selection of proteins of high biological value when qualitative limitation is indicated by the presence of allergy or quantitative limitation is necessitated by intestinal or other diseases It would, however, be a serious mistake to attempt to build practical human nutrition preferentially on foods containing "first class' proteins The production of animal proteins is relatively uneconomic and their price is accordingly high[36]

Mutual Supplementation of Dietary Proteins —Meat, fish milk and egg proteins, due to their complete amino acid composition and good digestibility, have a high biological value Most of the vegetable or grain proteins are low in some essentials such as lysine, tryptophan, threonine or methionine and therefore would not promote growth satisfactorily when fed by themselves Our meals, however, usually contain a mixture of different proteins with different amino acid compositions, such as those present in grains, vegetables and legumes Furthermore, they are as a rule consumed with some meat, fish or milk proteins It is self-evident that it is not the

* The digestibility of proteins and therefore the biological availability of their constituent amino acids can be determined with some degree of accuracy by *in vitro* digestion experiments

amino acid content of the single dietary proteins but the total supply of the necessary amino acids which determines the nutritive value of the ingested meal[37] It has been demonstrated that bouillon, containing gelatin, an incomplete protein, consumed with bread, improves the utilization of the grain protein by compensating for its low lysine content Cereals, legumes, roots, tubers, leaves, fruits, nuts and yeasts contain proteins which, by themselves, are mostly of low biological value Some of them taken together, however, may supply a satisfactory amino acid mixture due to mutual supplementation It has to be emphasized, however, that effective supplementation occurs only when the deficient and supplementary proteins are fed simultaneously or within a short interval of time[38] The timing in supplementation of deficient proteins represents a specific example of the importance of the time factor in protein synthesis which will be discussed in a later part of this chapter

The mutual supplementation of proteins has been practiced for ages but its mechanisms and importance has been recognized only recently The Chinese, for example, consume different cereals mixed in definite proportions and in this fashion they have empirically developed meals which contain protein mixtures of high biological value

The importance of the simultaneous feeding of supplementary proteins has been demonstrated in actual experiments in man Improvement in the utilization of breakfast cereals has been shown to occur when milk proteins are fed simultaneously[39] More recently it was reported that the complimentary proteins of corn and beans, the staple food of many Central American people, are better utilized when these foods are ingested together[40]

These findings would indicate that it is not absolutely necessary to feed *first class* proteins such as fish, meat, eggs or milk for maintenance of growth and good health The concept of supplementation also explains why certain religious groups or even whole populations living on strictly vegetarian diets do not necessarily suffer from amino acid deficiencies One practical implication of these findings is that in feeding of proteins of low biological value, as for instance in relief feeding or in emergency diets foods containing supplementary proteins should be fed together

As the world supply of complete animal proteins becomes increasingly short the economic significance of this concept is evident It shows also that, in devising therapeutic diets, it is not necessary to rely exclusively on the relatively expensive meat proteins In underdeveloped countries where protein deficiencies are endemic, the production of first class meat or milk proteins as is often suggested may disturb the economic structure, but a well-planned vegetarian diet based on the concept of mutual supplementation seems to be the logical solution of the protein problem

Very important studies on the use of plant protein mixtures in child feeding have been reported by Dean He found that certain combinations of barley wheat, and soy protein were "nearly perfect substitutes for all the milk in the diet" in feeding of children 1 to 2 years old[40a] Highly satisfactory results have been obtained also by the use of locally available plant protein mixtures in prevention and treatment of protein malnutrition particularly of Kwashiorkor in Africa and Central America[40b, 40]

Supplementation of Dietary Proteins with Synthetic DL-amino Acids — Another very promising trend is to improve the biological value of the deficient protein foods by supplementation of the missing or limiting amino acids with pure synthetic compounds[41] Methionine is already manufactured on a large scale and proved to be of value particularly in practical supplementation of low cost animal feeds, and recently great strides have been made towards the economic use of lysine and tryptophan for nutritional fortification The synthetic procedures currently used yield racemic compounds, and the resolution of these into optical antipodes in large scale production is not yet economically feasible, therefore, with the exception of recently introduced synthetic L-lysine at present only supplementation with DL-amino acids is practical This presents a problem in the use of synthetic DL-amino acids for human nutrition

Our natural food as well as the proteins of the human body contain only L-amino acids In most respects the D-amino acids behave differently from their optical antipodes[4] The peptide linkages in which D amino acids are involved resist gastro-intestinal digestion The intestinal absorption of D-amino acids is slower and, finally, only a few of them, such as D-methionine and D-phenylalanine, can be utilized by the human organism in lieu of the natural L-forms It seems that these two amino acids are first deaminated to the corresponding keto acids by a specific D-aminoacid oxidase present in some tissues, and the keto acids are then converted by transamination to the L-amino acids When all the essential L-amino acids are supplied with the diet then certain D-amino acids may be utilized for synthesis of non-essential amino acids[4,a]

Some of the D-amino acids are largely excreted in the urine after feeding It seems that most of these D modifications enter metabolic pathways different from those followed by the L-amino acids Their metabolism may therefore yield products with undesirable biological activity The fate of the D-amino acids will have to be further elucidated before practical, large scale supplementation of human food with the synthetic DL-compounds can be adopted safely

Comparable Nutritional Value of Animal and Vegetable Proteins[43]— It was shown in the preceding discussion that by proper selection and combination of plant proteins it is possible to devise meals which supply the necessary amino acids in satisfactory quantities The old nutritional belief that diets containing animal proteins are necessarily superior to those composed entirely of vegetable proteins is therefore valid only with qualifications This doctrine was originally based on several reports which showed that the bodily and mental development as well as health of human groups consuming foods of animal origin are generally superior to that of people adhering to strict vegetarian regimens[44] Several animal experiments also supported the idea that diets containing animal proteins are superior It was shown that on all vegetable diets, even when well supplemented, the growth of the animals was retarded and their reproduction damaged All these symptoms could be corrected by feeding small amounts of animal proteins Based on these observations the existence of a specific growth factor, the "animal protein factor" has been assumed Further investigations indicated that the animal protein factor is identical with

vitamin B_{12} (cobalamin)[45] and the presence of this vitamin was mainly responsible for the beneficial effects of animal food. Recent experiments suggest that animal food may contain some other as yet unidentified growth factors besides cobalamin. Thus, a study of the unsatisfactory vegetarian dietaries consumed by men show that it is not the vegetarian origin but rather the lack of some essential amino acids and specific factors which are responsible for the observed deficiencies. These diets can be improved by feeding supplementary plant proteins and by addition of the missing growth factors.

A second problem in the evaluation of an all vegetable diet is that, even by feeding mixtures of supplementary proteins, we cannot entirely simulate the amino acid composition of animal proteins. Evidently, although the essential ammino acids may all be available in a proper mixture of plant proteins, the relative concentration of the individual amino acids in the mixture may still be different. The importance of this *relative concentration* of the essential amino acids in foods for optimal growth and maintenance has been demonstrated in animal experiments. It has been shown that, if a given protein or amino acid mixture does not produce optimal growth because it contains only half the necessary amount of some essential amino acid, doubling the quantity of protein consumed will not promote optimal growth.[46] This may be the reason why diets containing large amounts of corn dishes, low in lysine and tryptophan, may lead to pellagra-like conditions even when the quantities consumed are adequate to supply the daily requirements of lysine and tryptophan. The importance of the relative concentration of amino acids present in food is further illustrated by the damaging effect of "amino acid imbalance."[47]

The concept of amino acid imbalance is based primarily on animal experiments in which it was demonstrated that excess of certain amino acids not only decreases growth but also produce metabolic disturbances. It was found that on force feeding of tryptophan free amino acid mixtures the animals were in worse condition than on force feeding of diets which did not contain any amino acids. The reason for this phenomenon is still unknown, and it is therefore evident that the often used slogan of "well-balanced amino acid mixture" merely disguises the lack of actual knowledge.

A further factor which may possibly lead to a better utilization of animal protein is the more favorable sequence and position of the individual amino acids within the animal protein molecule than in plant proteins. This difference may influence the enzymatic liberation and absorption of amino acids which, according to some authors, influences their utilization.[48]

We cannot yet predict whether it will ever be possible to bring up the nutritive value of vegetable proteins by supplementation completely to that of animal proteins. This, however, seems to be a rather theoretical problem because availability, price and personal preferences are more important in selection of protein foods than small variations in their biological value. Considering the many as yet unclarified differences between animal and vegetable food it seems safe to conclude that, in spite of the important practical results obtained in supplementation of diets containing only vegetable proteins, it is still good practice to provide, if possible, at least a fraction

perhaps one-fourth to one-half, of the daily protein intake in the form of animal proteins

PROTEIN REQUIREMENT OF MAN AND SOME FACTORS INFLUENCING IT

The minimum daily *protein requirement*, *i e*, the smallest amino acid intake which can maintain optimum growth and good health in man, can be approximated only crudely This is because short term investigations cannot possibly reveal late effects of insufficient protein intake, and long term experiments, requiring strict control of the diet, cannot be performed on men *living a normal life with any semblance of accuracy* *In short* term experiments the balance between dietary N-intake and urinary + fecal N-excretion has *frequently been studied, but this actually seems to be* a rather unreliable indicator of satisfactory protein intake The investigations of Allison[49] show that the quantities of protein necessary to maintain nitrogen equilibrium vary according to the nutritional status of the subject When the protein stores were exhausted even small amounts of absorbed N were sufficient to produce a positive N balance Likewise it was found that in patients on rice diets, nitrogen equilibrium could be maintained *with small quantities of protein—quantities which would not seem* to be conducive to good health [50] These latter results do not give much information regarding daily protein requirement, but, rather, indicate the poor nutritional status of the individual

Actually the optimal or average daily protein requirement of man would be a more important value to establish than the protein minimum "The task to obtain this information is a formidable one,"[51] and the sum of all the present data, including the National Research Council's recommended allowances "represent little more than intelligent guesswork as to the quantities of protein which will amply cover man's needs "

Dietary calculations are usually based on the "*Recommended Dietary Allowances*" published by the National Research Council These protein allowances are "considered to apply to persons normally vigorous and living in temperate climate" They are designed for good nutrition of healthy people in the United States They are based on 1 gm protein daily for each kg of desirable weight in adults *Some other recommended* allowances are for children, from 3 3 gm to 1 4 gm protein per kg daily, decreasing with age, for the last five lunar months of pregnancy add 20 gm daily during lactation, add 40 gm daily

The United States allowances seem to be somewhat high and can therefore be used safely, but *not economically*, as a basis for diet calculations

The *British* committee suggests that 11 per cent of the energy allowances in adults should normally be provided by protein and during growth, pregnancy and lactation, this should be increased to 14 per cent

The *Canadian Standard* relates protein requirement to the three-fourth power of the body weight on the assumption that protein requirement varies with body size (protein gm $2\ 75\ W_{kg}{}^{0\ 75}$)

The most serious shortcomings of all these calculations are (1) that they

do not take into consideration differences in the biological value of the different food proteins, (2) they do not consider the effect of mutual supplementation of simultaneously consumed proteins and (3) they evidently cannot take into account individual human variations

More adequate methods for defining human protein requirements have recently been proposed by a special F A O committee[5a] The calculations are based on a "reference" protein of high nutritional value such as present in eggs, milk, or meat It is assumed that this reference protein supplies all the essential amino acids in optimal proportions The quantities of the reference protein which are believed to represent the minimum requirement per kilogram of body weight are presented according to age of the person in Figure 2 of the report

According to these values the satisfactory protein intake in infants is approximately 2 3 gm during the early weeks falling to 1 5 gm per kg by the middle of the first year The requirements decrease with age but should be not lower than 0 8 gm /kg at puberty and 0 35 gm /kg for the adult

It is also suggested that an additional 10 g of protein should be consumed per day during pregnancy and that 20 gm extra protein may be needed to sustain lactation in the average woman

The committee recommends as *safe practical allowances* an arbitrary increment of 50 per cent over average minimum requirements For the period of infancy however an increment of 25 to 30 per cent seems to be sufficient When other than first class proteins are used the necessary quantities may be calculated by comparing the essential amino acid composition of the meal with that of the reference proteins Such comparison may reveal also which amino acid deficiencies have to be corrected by supplementation The F A O report represents the first up-to date official step toward assessment of human protein requirements However it still contains many provisional assumptions the nature of which are emphasized in the report It is therefore suggested that the pattern should be used only as a guide to the improvement of diets and that it should not be used mechanically without careful consideration being given to the overall nature of the diet under review

The assumption of some authors that the protein requirement increases in old age lacks any real basis Protein deficiencies observed in geriatric cases are usually the result of general poor nutrition Social economic and psychological reasons as well as disturbed mastication digestion and intestinal absorption may represent further aggravating factors[53,53a]

Specific Dynamic Action —The "specific dynamic action" was first described by Rubner who found that the consumption of protein rich food raises the metabolic rate by about 12 per cent of the ingested food energy The cause of this phenomenon has not yet been clarified in spite of many careful experiments and speculations A new lead was offered recently when it was found that the consumption of incomplete proteins leads to a higher specific dynamic action than does consumption of complete proteins[54] These experiments suggest that the metabolic transformation or the catabolism of those dietary amino acids which are not used for protein synthesis may be responsible for this phenomenon The assumption that

discarding amino acids present in excessive proportions is the causative factor is further supported by the finding that specific dynamic action does not seem to appear when ingested protein is used for growth and is deposited in the form of new tissue

In calculation of the protein requirement, the increment due to the specific dynamic action used to be considered in order to avoid possible deficits in protein supply It should be emphasized, however, that the importance of the *specific dynamic action* of protein in practical nutrition seems to be highly overrated "Practically nothing is known about it in human beings under ordinary conditions of activity and everyday living, and under normal food consumption at the usual intervals "[55] It therefore does not seem to be necessary to make special allowances for the specific dynamic action in calculation of the daily protein quota, especially because the "recommended allowances" already include a liberal overdose Furthermore, the increment of the metabolic rate is definitely *not* large enough to justify the often made assertion that a high specific dynamic action is primarily responsible for the "not fattening" or reducing effect of protein food

In connection with diet calculations one must also consider that *physical activity* does not significantly increase the protein requirement

Effect of Other Food Ingredients on Protein Utilization —In the foregoing sections human protein requirements were considered only with respect to amino acid composition, digestibility and some other properties of the dietary proteins themselves Obviously, protein synthesis, growth and repair can occur only when the organism is supplied with other essential nutrients such as vitamins and some inorganic substances Another fact recognized as important long ago, but now too often forgotten, is that, in the absence of adequate caloric supply in the form of carbohydrates and fats dietary amino acids cannot be utilized efficiently This old rule already recognized by Voit has gained increased significance recently because it has become therapeutic practice to administer protein concentrates or amino acid preparations *only* in cases where normal food intake is disturbed This practice is based on the misconception that an adequate supply of amino acids by itself can prevent the destruction of body proteins Another reason for the recent prominence of this problem was the search for satisfactory survival rations in combat emergency[56] These recent investigations have shown, in perfect support of earlier findings, that protein cannot be utilized for growth or maintenance nor can it prevent breakdown of tissue protein when the diet does not provide satisfactory quantities of other energy sources such as carbohydrates and fats This happens because the *energy requirement* of the organism has to be satisfied *first* In starvation, in cases of restricted caloric intake, as in famine or in reducing diets, the necessary energy is obtained by breakdown of tissue substances, including tissue protein In cases where only proteins or amino acids are fed these are metabolized into energy yielding compounds and the nitrogen which is split off is excreted "It was found therefore that in people on severely restricted diets in general the nitrogen retention was proportional to the caloric input but not proportional to the nitrogen input" (Quinn) Most of the investigations seem to indicate that unless

about 50 to 60 per cent of the caloric requirement is satisfied by fat or carbohydrate the amino acids cannot be used for protein synthesis or other specific purposes Accordingly, even the addition of 43 gm of high grade protein such as egg albumin to a diet supplying a total of only 950 calories failed to improve the nitrogen balance of healthy adults over the group receiving a similar diet without protein These results lead to the practical conclusion that proteins and amino acids should not be fed by themselves, *e g*, proteins "should be left out of any survival ration which provides for a daily intake of 900 calories or less "[57]

It also seems questionable whether feeding of relatively large amounts of protein with severely restricted low caloric reducing diets will protect body protein from destruction, in fact, loss of body protein on such diets has been demonstrated[58]

In addition to their calorigenic action, carbohydrate and fat probably also have specific effects on protein metabolism[59] Carbohydrate seems to be more effective, however when carbohydrate is provided by feeding about 150 to 200 gm of sugar, consumption of fat seems to exert an additional beneficial effect[60]

The nitrogen sparing action of sugar is most effective when it is consumed simultaneously with the protein The timing seems to be very important, because, when sugar is fed more than four hours before or after the protein meal, it loses its maximum protein sparing action As to the mechanisms by which carbohydrate and fat promote protein utilization apart from their calorigenic sparing action several factors have to be considered[61] Special attention has to be given to the retarding effect of these foods on gastro-intestinal dynamics, including gastric emptying time, secretion, motility and absorption The prolonged digestion and protracted rate of amino acid absorption could well improve the utilization of dietary proteins Another factor to be considered is that simultaneously fed sugar may promote protein synthesis by providing easily available precursors for rapid synthesis of some missing nonessential amino acids Such an effect is suggested by the increased retention of ammonia, after feeding of labeled ammonium citrate when animals receive glucose, indicating that simultaneously fed sugar may expedite the utilization of ammonia nitrogen for amino acid synthesis[6]

The effect of intermediary fat and carbohydrate metabolites in the metabolic phase of amino acid utilization also seems to be very important This has been indicated by results of experiments in man where simultaneous intravenous injection of a glucose solution considerably improved the utilization of injected amino acid mixtures[63] Glucose also protects amino acids from breakdown Thus it was found that, when glycine is given with sufficient amounts of sugar it is largely retained instead of being rapidly converted to urea[64] It was also observed in test tube experiments that intermediary products of fat and carbohydrate metabolism, such as lactate, pyruvate and succinate, inhibited the deamination of amino acids Finally, carbohydrate and fat metabolites may provide some necessary links for the phosphorylation of amino acids or for other energy consuming steps involved in the synthesis of body protein

Effect of Excessive Amounts of Protein in Diet.—The amino acid requirements are high in infancy, childhood, adolescence and during pregnancy because large amounts of proteins are newly formed in the rapidly growing tissues. Synthesis of milk proteins during lactation and growth of muscle tissue in the course of athletic training also increase the adult requirements. Similarly, replacement of lost tissue during convalescence after consumptive diseases or during rehabilitation following malnutrition requires an ample supply of dietary amino acids.

The utilization of dietary amino acids for protein synthesis is limited by the actual requirements of the body for growth and maintenance.

Protein, unlike fat, cannot be stored in appreciable quantities, therefore, dietary amino acids which have been consumed in excess of the requirements are further metabolized, *i.e.*, after decarboxylation they enter the common mill by which carbohydrates and fats are utilized.[65] It is therefore not economical to feed relatively expensive high protein foods in abnormally high quantities.

The question whether consumption of excessive amounts of proteins has any harmful effect cannot be answered without qualification. It is well established that Arctic explorers and other persons kept on well-controlled diets subsisting for many years mainly on meat, do not develop any pathological symptoms. We can therefore conclude that normal adults seem able to tolerate the intake of amounts of protein far above actual requirements. Infants and children, particularly those not adapted to high protein foods, do not do well on diets containing large amounts of protein.[66] It is therefore recommended by several authors that the protein intake be increased only gradually. This suggestion has to be considered particularly in connection with rehabilitation diets given after malnutrition.

The idea that excessive protein intake may lead to development of, or aggravate already existing hypertension, or that it may cause toxic complications in pregnancy has been abandoned.[67] The assumption that protein food, due to its calorigenic specific dynamic effect, may adversely influence the course of febrile diseases also proved to be false. The consideration that large amounts of protein may damage the kidneys or liver has never been supported by observations in man. Even the exclusion of protein from the diet of people with developed liver or kidney damage is an obsolete practice. More recent studies have shown that diets containing ample amounts of protein very often improve the healing tendency in liver or kidney diseases. Therefore, hypertension, febrile diseases, kidney or liver ailments are no longer considered generally as contraindications to protein rich diets. On the other hand, they should not be regarded as indications for feeding excessive amounts of protein, which has often been suggested with the idea that "enough protein is good, but more may be even better." There is no wisdom in prolonged feeding of diets which contain more protein than 20 per cent of the total caloric intake. Clinical observations suggest, and animal experiments prove, that in certain specific types of liver disturbance feeding of unduly high amounts of proteins may aggravate the disease by overtaxing liver functions involved in utilization of dietary amino acids.[68] It is also self-evident that in kidney diseases where the danger of accumulation of protein end products, increase of

blood NPN, is imminent, the protein intake should be restricted or even temporarily eliminated Finally, in some cases of metabolic disturbances such as cystinuria, phenylketonuria, alkaptonuria and gout protein restriction may be of therapeutic value[69]

FATE OF ABSORBED DIETARY AMINO ACIDS

Dynamic Equilibrium Between Tissue Proteins and Dietary Amino Acids —The amino acids absorbed in the intestines are carried with the portal blood to the liver[70] Some of them are retained there to satisfy the specific requirements of this organ the rest enters the general circulation, from which they are rapidly removed by the several tissues This uptake, which may occur against concentration gradients as high as 1 9 seems to involve specific, selective mechanisms[71] The liver and the kidneys are the most active in removal, while skeletal muscle is less efficient The brain does not show any detectable uptake The fate of the amino acids in each tissue varies according to the momentarily prevalent requirement In starvation or semistarvation the dietary amino acids are utilized primarily as a source of energy in order to minimize the caloric deficit of the organism If enough non-protein calories are provided with the daily food intake the amino acids are utilized for specific purposes such as the synthesis of proteins and of biologically active polypeptides or peptides *e g* the synthesis of oxytocin enzymes glutathione or carnosine The amino acids may also be directly transformed into other physiologically important compounds such as epinephrine, creatine taurine and many others

Besides these well recognized functions, the dietary amino acids participate in the still highly enigmatic process of "dynamic equilibrium" which exists between tissue proteins and dietary amino acids This phenomenon was first suggested by the fundamental experiments of Schoenheimer, who showed that when labeled amino acids are fed the labels are incorporated relatively rapidly into the proteins of the different tissues In these experiments he demonstrated that the tissue proteins are not rigid structures but that there is a steady 'give and take between tissue protein and dietary amino acids This revolutionary new concept contradicted most of the earlier theories, which had assumed that tissue proteins do not regularly enter metabolism systems but instead are used up slowly by the daily "wear and tear'—whatever this expression means According to the old theory, tissue proteins are mobilized only when the exogenous supply *i e* the dietary amino acid intake is deficient Before Schoenheimer s classic experiments Borsook and Keighley s investigations already indicated a *continuous metabolism* of tissue proteins even when exogenous protein supply and food intake were satisfactory[7]

Schoenheimer and collaborators found that the rate of labeled amino acid incorporation is not equal for every tissue but depends on the life span of the particular tissue proteins Tissues containing short lived proteins show a rapid turnover *i e*, they take up and lose labeled compounds fast That the uptake of dietary amino acids parallels the metabolic rate is indicated by the fact that fetal tissue tumors and rejuvenating organs in-

corporate labeled compounds faster than do normal adult tissues Schoenheimer s original assumption that all body proteins participate in the dynamic equilibrium has recently been modified by investigations which show that only about 30 per cent of human carcass protein is involved in the dynamic state while the rest is relatively or absolutely unreactive[7] Experiments on amino acid uptake by different tissues under varying conditions have supplied a large volume of most interesting but somewhat incoherent data We have to expect that these investigations will discover some as yet unknown functions of protein as part of living protoplasm

The ease with which labeled amino acids are incorporated into some tissue proteins forecasts a drastic revision of the current concept of the rigid structure of living protein At present it is difficult to visualize how and why peptide bonds of preformed tissue proteins should be steadily cleaved and reformed—a process which seems to be a prerequisite for the incorporation of dietary amino acids into tissue proteins

Biosynthesis of Proteins—Dietary amino acids supply the material necessary for protein synthesis, for growth and for adult requirements Feeding experiments indicate that for optimal protein synthesis all constituent amino acid must be present simultaneously and in adequate quantities If one or more of the essential amino acids are missing or are not supplied in satisfactory quantities, the rest of the amino acids which have not been utilized for protein synthesis are irreversibly metabolized Such dietary excess amino acids can neither be stored in the body nor used for formation of partial building stones (plasteins) from which protein synthesis could proceed eventually Any delay in supplementation of the missing amino acids decreases utilization so that, when 4 to 6 hours intervene between feeding the incomplete mixture and the missing amino acids, there is detectable interference with protein synthesis[4] Single labeled amino acids disappear from the metabolic pool within four hours[73] These findings have significance not only for practical nutrition, but, as shall be discussed later they also supply suggestions concerning the mechanism of intravital protein synthesis

As to the mechanism of protein synthesis, there are presently two theories[6] According to one the so-called plastein theory, "the newly formed proteins are synthesized piece by piece," *i e*, first short peptides are formed from the amino acids and these smaller units, the "plasteins" are then connected successively to yield a protein molecule It has been demonstrated several times that peptides can be formed by the reversed action of proteolytic enzymes but this piece-by-piece synthesis can hardly account for the structural and immunological specificity of the newly synthesized proteins Another objection to the plastein theory is that the presence of a large variety of specific peptidases would be necessary in the different tissues in order to form the large variety of peptides present in different proteins The production of plasteins in the course of protein formation has never been demonstrated, however, it is possible that such intermediary products have not been isolated and identified because of their short-lived transient existence[77] Finally, the plastein theory could not explain the importance of the time factor in feeding of amino acid mixtures According to the other hypothesis, the "template theory,"

proteins are formed as replicas of templates or molds so that the specificity of the template determines the specificity of the newly formed protein According to this concept, protein synthesis is an "all or none" affair When, because of lack of some building stones, the protein cannot be synthesized the rest of the amino acids are released from the template and thus enter the metabolic mill

The results of experiments on the uptake of labeled amino acids by tissue proteins are often used as an argument against the "all or none' mechanism and in favor of the plastein theory of protein synthesis The argument is that growing tissues, *in vivo* or *in vitro* incorporate single tagged amino acids not only when fed simultaneously with the others but also when such are made available alone This observation, however indicates only that the anabolic tissue building mechanisms cannot distinguish between labeled and unlabeled amino acids and that either one may be included at random depending on its relative concentration in the medium Further evidence against the hypothesis that a direct relationship exists between the uptake of amino acids and protein synthesis is obtained from experiments which demonstrate an *increased* uptake of labeled amino acids by the tissues of animals on protein free diets, under these conditions there can be *no* synthesis of new protein molecules Likewise tissue culture experiments show a more rapid uptake of labeled amino acids under conditions which favor tissue breakdown rather than tissue synthesis Finally it should be emphasized that there are only a few published cases in which it has been established by reliable methods that "uptake' actually represents incorporation of labeled amino acid into tissue protein by newly formed peptide linkages At present neither the plastein nor the template theory is sufficiently developed and therefore neither one can explain all the different phenomena observed in connection with protein synthesis [78] The experiments on the importance of the time factor in feeding amino acids however seems to support strongly the all or none template theory

The simultaneous supply of amino acids is important not only for growth but also for adult maintenance Although a steady give-and-take occurs between tissue proteins and dietary amino acids it would seem that aging protein molecules cannot be mended through piece-by piece replacement of individual amino acids Protein molecules used up in the daily ' wear-and tear have to be replaced by a synthesis which like growth requires the simultaneous presence of all the requisite amino acids According to some recent calculations in a normal adult about 1 3 grams of protein is synthesized per kilogram of body weight per day *i e* 91 grams for a 70 kilogram man [73] The amount of protein built up for so-called adult growth as formation of hair, nails secretions, hormones and enzymes is quantitatively negligible Most of the proteins synthesized in the adult under physiological conditions serve to replace tissue proteins actually broken down in connection with the life processes The proteins of the different tissues are not replaced to the same extent The ' turnover rate as determined with tagged amino acids indicates that the necessity for replacement varies according to the function of the different organs Thus, the half life of serum and liver proteins is approximately ten days while that of hemoglobin is twenty-five to thirty days and that of muscle protein

is about one hundred and eighty-five days. Even within a given organ, for instance the muscle, the turnover rate may be very different for the different protein fractions. The highest *rate* of protein formation has been found in the pancreas and in the intestines, *i.e.*, in the organs which constantly lose newly formed proteins with their secretions.

Quantitatively, however, the most active site of protein synthesis is the liver. In addition to producing liver protein, it is also the main site of plasma albumin and fibrinogen synthesis. Serum globulin seems to be chiefly synthesized extrahepatically.

It is often assumed that plasma albumin is a transport form of protein during passage from the liver to the tissues. In experiments on the isolated mammary gland it has been shown that albumin can actually be used for synthesis of milk proteins but only after degradation to amino acids.[79] Transfer of larger fragments, such as peptides produced by breakdown of albumin, to the newly formed milk protein does not seem to occur. It appears that plasma albumin, which has to fulfill other physiological functions, serves only occasionally as a source of amino acids for protein synthesis.

The main source of raw materials for protein formation in the tissues are the amino acids present in the tissue fluids. These include the absorbed dietary amino acids, in addition to some nonessentials which are newly formed in the body and the amino acids liberated during the breakdown of tissue proteins. Recently it has become customary to refer to this mixture of amino acids present in the different tissue fluids as the *"metabolic pool"* of amino acids. This is done in spite of the fact that recent experiments actually disprove the existence of a single homogeneous metabolic pool in the body.

Besides synthesis of proteins, the amino acids are used for formation of smaller peptides whose biological significance is not well understood at present. A list of such peptides must include *glutathione*, a tripeptide of glutamic acid, cystine, and glycine, *anserine*, containing β-alanine and histidine, and its methylated analog *carnosine*. The major physiological problem, *viz.*, which factors initiate and determine the extent of this peptide synthesis is unsolved.

Metabolism of Amino Acids.[2]—The general metabolic fate of amino acids is determined by their common structural elements. A terminal carboxyl group and an amino group in the α-position* is characteristic of the amino acids naturally occurring in proteins. *Only proline and hydroxyproline* containing an imino group form an exception. Due to this general structure the amino acids can participate in several bioprocesses, including peptide and protein synthesis, deamination, decarboxylation. Peptide and protein synthesis have been discussed in earlier parts of this chapter (p. 114).

Deamination.—The first step on the regular pathway of amino acid catabolism is usually *deamination*. In this process the basic amino group is split off and thus the amphoteric monoamino acids are transformed into α-keto acids. Deamination in animals is an oxidative process and

* In the human and animal tissues β-alanine is present in carnosine, anserine and pantothenic acid. It may arise by decarboxylation of aspartic acid.

the elimination of two $-NH_2-$ groups requires the uptake of 1 mole of oxygen This deamination is accomplished by amino acid oxidases which are present in largest quantity in the liver and kidneys and which require as coenzyme the presence of flavo-proteins The importance of the liver in deamination has been demonstrated by the fact that in hepatectomized animals and in acute liver atrophy in man deamination is seriously disturbed The deaminases or amino acid oxidases are highly specific they act only on the L-amino acids Although the presence of large amounts of the d amino oxidases in the organism has been established, their physiological role has not yet been recognized because under normal conditions D-amino acids are neither taken in with the food nor produced in the body Some of the amino acids require the action of specific deaminating enzymes *e g* the existence of specific enzymes for selective deamination of glycine and glutamic acid has been demonstrated

Urea Formation —The liberated $-NH_2$ can be utilized for production of other amino acids by transamination of their precursors Most of it however is transferred into the metabolic channels of *urea formation* Recent investigations indicate that much of the $-NH_2$ groups may be transported from the amino acids to the urea channel without going through the stage of free ammonia This transport occurs in form of glutamic or aspartic acids or their derivatives which take up the $-NH_2$ split off from amino acids

The mechanism of urea production from ammonia has been elucidated by Krebs and Henseleit in their brilliant experiments on the *rnithine cycle* Borsook and Dubnoff, as well as Ratner enriched this basic oncept with further important findings According to the evidence upplied by these authors urea formation occurs in three main phases

1 The amino group produced by deamination is transferred to *ornithine* This compound takes up $-NH$ CO_2 and H_2O simultaneously to be converted into *citrulline* Details of the enzymatic citrulline-formation are still under study It seems that a derivative of glutamic acid, possibly carbamyl glutamic acid is involved as a donor of the necessary NH_3 and CO_2

2 In the next step citrulline receives a further $-NH_2$ group from aspartic acid by transamination This amino group was also derived originally from deamination of amino acids Citrulline is thus transformed into *arginine*

3 As a final step, an enzyme called "arginase splits arginine into urea and ornithine by hydrolysis

Urea is excreted in the urine and ornithine re-enters the cycle for more urea formation The most important steps of urea formation seem to occur either in the liver itself or elsewhere with the help of enzymes produced by the liver Formation of urea has never been observed after hepatectomy

As is well known urea is the main nitrogen containing end-product of our protein metabolism excreted in the urine Normally a small amount of ammonia in the form of ammonium salts is also excreted This ammonia production is increased in acidosis probably in order to neutralize the acids produced in intermediary metabolism The source of urinary ammonia is blood glutamine which carries the NH_2 group produced by deamination of

amino acids to the kidney, there ammonia is liberated enzymatically according to the prevailing requirements Finally, considerable amounts of nitrogen, originating at least in part from amino acids, are excreted in the form of uric acid and creatinine

Decarboxylation [80]—An alternate pathway of amino acid catabolism is *decarboxylation* whereby the pharmacologically inert amino acids are transformed into for the most part highly active amines Decarboxylation itself involves the splitting off CO_2 and the enzymes which perform this reaction seem to be highly specific for each amino acid With the exception of histidine decarboxylase all others require the participation of pyridoxal-phosphate as co-enzyme Decarboxylation by intestinal bacteria was recognized early and the increased formation of *putrescine* from ornithine, of *cadaverine* from lysine, *histamine* from histidine, and *tyramine* from tyrosine in the intestinal tract was often considered a sign of pathological putrification It was also assumed that the formation of these toxins leads to "intestinal autointoxication" It was shown later, however, that under normal conditions the intestinal wall and the liver can detoxicate most of the amines which may be absorbed from the gut

Not only the intestinal flora but also many tissues have the ability to convert amino acids into amines by decarboxylation Thus the kidneys and especially the liver, seem to be responsible for the formation of amines such as *tryptamine* (β-indolethylamine) from tryptophan, of *tyramine* from tyrosine, and possibly also of *histamine* from histidine The presence of large amounts of glutamic acid decarboxylase was discovered in the brain tissue This enzyme removes only one carboxyl group from the dicarboxylic acid to produce α amino butyric acid instead of an amine

Another biologically important group of amines results when the decarboxylation is preceded by some other metabolic changes in the original amino acid molecule From cystic acid a cystine derivative, *taurine*, is produced by decarboxylation Hydroxy-tryptophan is decarboxylated to *hydroxy-tryptamine* This substance also called "serotonin," is present in the blood and is possibly connected with the development of some types of hypertension *Nor-adrenalin*, a hormone produced by the adrenal medulla seems to be a decarboxylation product of dihydroxy-β phenylalanine, the latter constituting an oxidation product of phenylalanine Nor-adrenalin is further transformed to *adrenalin*, by methylation, involving the methyl group of methionine The formation of some other amines in the body such as *ethanolamine* and *spermine*, has also been established It is to be expected that the number of known amines formed in the human body from amino acids or their derivatives will increase as analytical methods are further refined The large number of the so-called *biogenic amines*[81] in different living organisms and their pharmacological activity suggests that some symptoms of infectious diseases may be brought about by amines produced by the infective micro-organisms The pathogensis of some other diseases may be also connected with the action of amines produced in the disturbed intermediary metabolism

Upon decarboxylation or deamination these compounds lose their character as amino acids The further metabolic fate of most of the derived compounds is closely linked to that of fats and carbohydrates Certain of

these such as the amines the imidazol- the sulfur- the indol- and the phenolic compounds formed from amino acids, require specific enzyme systems for further metabolic changes It was shown a long time ago that the keto acids produced by deamination of amino acids participate either in glycogen in fat, or in ketone body formation However, the classification of amino acids as glycogenic or ketogenic substances seems to be too rigid and perhaps obsolete in the light of recent biochemical research

Transformation into Other Compounds —Besides participating in protein syntheses, the amino acids are utilized by the organism also as precursors of some *hormones, vitamins co-enzymes* and other compounds As mentioned above, the amino acids have to be present simultaneously in the interest of effective protein synthesis, this statement does not imply however, that an individually fed amino acid cannot be utilized by the organism for some other purposes *e g*, conversions into other compounds Such so-called *"extraprotein functions"* of the amino acids can often be differentiated experimentally from the 'protein function' by observing the effects after feeding a particular amino acid simultaneously with or apart from the other amino acids For example it was found that some symptoms of amino acid deficiency can be eliminated even when the missing amino acid is fed by itself as a delayed supplement, *i e*, when it does not promote protein synthesis Thus tryptophan promotes niacin formation and cures niacin deficiency even when fed alone Similarly methionine displays its lipotropic effect even when fed apart from the other amino acids

A review of the immense literature on *transformation of amino acids* *nto other compounds* will not be attempted here In the following e intend to discuss only such conversions which according to our present ncepts lead to the formation of physiologically or pathologically important compounds From this point of view, *phenylalanine* seems to be most interesting subject Phenylalanine and tyrosine which is formed oxidation of the phenol ring in para position are precursors of two types of hormonal substances The formation of *nor-adrenalin* and *adrenalin* in the adrenals by decarboxylation has already been discussed The iodination of tyrosine to *monoiodo-* and *diiodo tyrosine* and their condensation by the thyroid cells to *thyroxine* and *triiodo-thyronine* is currently the subject of numerous investigations *Melanine* a dark insoluble pigment normally present in the skin in the hair and some other tissues also seems to be formed from phenylalanine[8] under physiological conditions This process is decreased or absent in *albinism* Abnormally large quantities of melanine are formed or accumulated in certain tumors such as *melanomas* or excreted with the urine in *melanuria*

Phenylalanine and tyrosine may enter different metabolic pathways and several phases of these may be blocked by damage of the liver, or by hereditary gene linked 'metabolic errors,' or even by some vitamin deficiencies Impaired phenylalanine metabolism in cases of liver damage leads to *phenylketonuria* In such cases because of the disturbed oxidation in the benzene ring some other products of imperfect metabolism such as phenyllactic acid are also excreted Besides disturbed oxidation the ultimate breakdown of the ring structure is also abnormal and hence p-hydroxy-phenylpyruvic acid is also found in such urines

Scorbutic guinea pigs and some premature children excrete similar compounds in their urines, in such instances large doses of ascorbic or folic acid may correct the metabolic disturbance There are, however, cases where not a lack of vitamins but rather a hereditary derangement of the enzyme system is responsible for the "metabolic error", *e g*, the phenylpyruvic acid excretion observed in *Folling's* disease ("oligophrenia phenylpyruvica") Here the accumulated products of imperfect phenylalanine metabolism lead in turn to disturbances of the brain metabolism and to mental defects [63] Although the administration of vitamins is then of no value the restriction of dietary phenylalanine and tyrosine shows at least transitory salutary effects on the mental condition

In another inborn metabolic error, *alkaptonuria*, 2-5 dihydroxy-phenyl acetic acid (*homogentisic acid*) is excreted in the urine The latter turns dark when standing in air at alkaline reaction because a dark pigment is formed The same compound is deposited in *ochronosis* and in some cases of *osteoarthritis*

A very versatile amino acid is *glycine* It is a constituent of the tri peptide *glutathione*, it participates in the biosynthesis of a bile acid *glycocholic acid* it is utilized for the formation of *purines*, of *uric acid*, of *porphyrines*, and may be converted into other amino acids such as *serine* or *cystine* It is conjugated with benzoic acid to *hippuric acid* Finally, it participates via glycocyamine in the formation of *creatin* Glycine was therefore rather widely used as a roborant in muscular weakness, however critical investigation proved the ineffectiveness of such "therapy " Glycine when administered to animals in large doses produces toxic symptoms This effect can be prevented by the simultaneous intake of large amounts of vitamin B_1 and/or of folic acid These observations indicate the existence of some further unknown features in the intermediary metabolism of glycine

The results of intensive investigations of the bio-transformation of *tryptophan* into *nicotinic* acid have shown that it involves numerous intermediary steps The use of tryptophan in pellagra is not practicable because of its high price compared with that of niacin These studies have indicated, however a fact already recognized by Goldberger in his classic investigations, *viz*, that the dietary supply of first-class proteins containing sizable quantities of tryptophan is the most important factor in the prevention of pellagra

The discussion of *methionine* seems to be particularly interesting because its therapeutic use in liver diseases was widely recommended as recently as a few years ago This suggestion was based on experiments on animals in which liver damage with fat deposition was produced by inadequate diets In such cases addition of methionine to the diet had a beneficial, *lipotropic* effect, it removed the accumulated fat from the liver and when given in time also reversed the liver damage Some clinical investigators encouraged by these experiments on animals prescribed synthetic methionine in human liver diseases These reports, at first enthusiastic, turned out later to be not too encouraging Methionine proved to be of little value in nutritional liver disease such as Kwashiorkor The contradictory reports concerning the methionine effect on some other liver diseases indicate that

the therapeutic effect, where it can be definitely shown, depends on the pathogenesis of the liver disease. Methionine treatment seems to give reliable results only when the liver has been damaged by a specific, experimental methionine deficiency. In fact recent studies indicate that in some clinical cases methionine utilization by the damaged liver is disturbed.

Methionine can be transformed to cystine and as a methyl donor it participates also in the biosyntheses of choline, creatine, adrenalin and sarcosine, the latter being a methyl derivative of carnosine (β alanylhistidine). The importance of methionine in transmethylation processes first demonstrated in Du Vigneaud's[84] important investigations has recently been somewhat reduced. It was shown that vitamin B_1 and folic acid administration promote the production and the transfer of labile methyl groups and therefore decrease the methionine requirement. In connection with these investigations it was also shown that methionine itself can be produced in the body after feeding its methyl-free precursor, *homocystine*, and satisfactory amounts of cobalamin (B_{12}).

Urinary Excretion of Amino Acids.—After feeding protein foods the gradual digestion and absorption so operate as to yield only a small increase in the amino acid concentration in the blood. Even on feeding or intravenous injection of amino acid solutions there is only a transitory increase of the blood amino acid concentration. However, the plasma and the tissues contain in the late post absorptive stage or at starvation also a certain amount of free amino acids. It is not yet clear whether these are merely in the state of regular transport from one tissue to another or whether they are essential homeostatic constituents. The blood amino acids are filtered or excreted in the glomeruli and are reabsorbed in a highly selective manner by the renal tubuli.[85] The renal threshold values for the individual amino acids are therefore rather different. The urine contains under normal circumstances some amino acids, both in free and in conjugated form. The total daily excretion is on the average 160 mg for a normal adult, i.e., less than 1 per cent of the total daily amino acid intake.

If the amino acid concentration in the blood increases over the threshold level as after ingestion or rapid injections of concentrated amino acid solutions an *alimentary* amino aciduria develops. In mice and rats after feeding incomplete proteins one part of the amino acids which are not used for protein synthesis or for production of other specific compounds is excreted with the urine. In man however the amino acid content of the urine seems to be widely independent of the quality of the protein present in the food.[86]

Pathological amino acidurias develop either as a consequence of disturbed renal tubular reabsorption or as sequela of disturbed amino acid utilization. The most important forms of renal amino aciduria are *cystinuria*, *tyrosyluria* and the *chronic amino acidurias* of children as a part of the Debre-de Toni-Fanconi[87] syndrome. Cystinuria, which was earlier regarded as a metabolic error with hereditary trait, is now thought to be caused in most instances by disturbance of tubular amino acid reabsorption. This assumption is supported by the finding that in such cases in addition to cystine usually large amounts of other amino acids such as arginine, ornithine and lysine can be detected in the urine. In-

creased urinary excretion of cystine, because of its low solubility, may lead to secondary kidney damages or to urinary stone formation (see Chapter 25)

Amino aciduria observed in *galactosemic* children seems to be the consequence of the metabolic disturbance because chronically increased blood galactose concentration by itself does not interfere with the renal reabsorption of amino acids [88]

Chronic amino aciduria of children, a recessive hereditary disease, usually *develops at the age of two to six years and leads to death* before the age of eight Concomitant symptoms are, glycosuria, vomiting, adynamia, polyuria, tetany, dwarfism and rickets Due to the urinary loss of essential amino acids liver damage and anemia develop in such cases Disturbed renal function and deamination, with consequent accumulation of amino acids, are responsible for the development of this syndrome

Amino aciduria has also been observed in some cases of hepatic insufficiency This occurs because normally the liver is the most important organ for amino acid catabolism, and inadequate deamination by the diseased liver may lead *to an abnormal increase of the blood amino acid con*centration to levels exceeding the kidney threshold level [89]

A peculiar type of amino aciduria was observed in Wilson's disease, in hepatolenticular degeneration The amino aciduria in Wilson's disease is characterized by the excretion of oligopeptides, *i e*, peptides containing only a few amino acids, these are eliminated because their splitting by carboxypeptidases seems to be inhibited The liver cirrhosis observed in Wilson's disease seems to be the consequence of the urinary loss of essential amino acids[90] (see Chapter 10A)

PROTEIN ANABOLISM AND CATABOLISM

Protein *anabolism* and *catabolism* are terms widely used to indicate protein synthesis or breakdown in the organism These terms have lost *much of their exact meaning since we now know that 30 to 50 per cent of* the total body protein is in steady flux, that is, under physiological conditions breakdown and new formation, anabolism and catabolism of the tissue proteins are occurring simultaneously and are well equilibrated in the normal adult However, it is still widely held that the intensity of the anabolic or catabolic processes can be measured by determining the net balance of the N-equilibrium In this connection it must be remembered that "nitrogen balance is the sum of the gains and losses of N from the various compartments of the body It is possible for an animal to be in positive N-balance and yet depleting some labile stores in protein" (Allison) An intense or torpid breakdown may well be balanced by an increased or sluggish protein synthesis or vice versa and thus may not affect the N-excretion at all The N-excretion can be influenced by many factors so that even in cases when N-balance is shifted decidedly to the positive or negative side the results should be carefully evaluated N-retention does not necessarily mean that new tissue-protein is being synthesized Thus for instance, in myxedema after cessation of thyroid therapy N is retained positive balance is established, but evidently the retained N has not

been used for tissue-building anabolic processes but rather for a pathological accumulation of proteinaceous material in tissue fluids.

Recent attempts to determine the anabolic or catabolic tendency by following the speed of uptake of labeled amino acids are of big heuristic value and very promising but the conclusions arrived at by such methods are presently still open to criticism. The main objections are discussed at other points in this chapter.

Anabolic Conditions.—Total anabolism outweighs total catabolism during growth, during rehabilitation after disease or malnutrition, in the later part of pregnancy and also during physical training when new muscle tissue is formed. In such cases of N retention a positive N-equilibrium can be easily demonstrated. There are, however many cases where anabolism is restricted to only one or a few organs or tissues and therefore the protein synthesis is not reflected in a positive over all nitrogen balance.

It is an important biological rule that in the formation of new tissue protein primarily for growth or repair, it is the anabolic growth or healing tendency of the cells and not the dietary supply of building stones which determines the speed and extent of protein synthesis. Growth or repair may occur in spite of an over-all negative N-balance. In such cases simultaneous catabolism induced in other organs may provide the required amino acids for the growing tissue. The first classic example was described by Miescher [91] who found that the salmon while migrating in fresh water to its spawning grounds does not consume food. The generative organs are in spite of starvation rapidly increasing in weight and this occurs at the expense of muscle substance which is metabolized during the migration. Other examples are pregnancy or lactation where in cases of inadequate protein intake body substances of the maternal organism may be broken down in order to provide building stones for the growth of the fetus or for the synthesis of milk proteins. Similar conditions can be observed during regeneration of organs which atrophied due to transient inactivity and also in wound healing. Further examples are, rapidly growing tumors which obtain building blocks for protein synthesis from the breakdown of normal tissues [9]. In all these cases it is the anabolic growth repair or healing tendency of the tissues and not the dietary supply which determine the speed of protein synthesis. It was found that protein feeding or amino acid injection does not significantly accelerate the reparative processes in wound healing which proceed normally at least for a period of a few days even when protein starvation prevails. It is evident that feeding protein as soon as possible improves the general condition primarily by replacing the mobilized proteins in the donor tissues.

These observations raise two interesting problems. The first one is the non-dietary source of protein which is utilized for promotion of growth or tissue regeneration and the second problem is the identification of the signals which initiate the mobilization and transfer of tissue protein from other organs to the growing tissues. It seems to be well established that the body does not possess protein stores containing specific 'inert fractions' of body protein which have the primary function of being available in cases of such emergencies [93]. All phenomena can be satisfactorily explained by the assumption that part of the normal tissue protein can be mobilized to sup-

port growth or repair in some other organs Liver protein seems to be particularly available as an amino acid source [94] It was demonstrated, *e g*, that in dietary protein deficiency the liver loses 20 to 40 per cent of its total protein content within a few days, the remainder resists further mobilization This does not mean, however, that the easily available liver protein represents an inert storage protein fraction The liver is not the only organ able to furnish amino acids in case of increased need It was shown that after partial liver extirpation, for instance, other tissues *may provide the building stones necessary for regeneration of the liver itself*

It is customary to designate the sum of the more easily available protein fraction present in many organs as "protein stores" without any prejudice to their structural specificity or physiological importance There is at present no way to measure how much of the total body protein can be mobilized without functional interference

The second problem concerns the stimuli which notify the donor tissues of the prevailing amino acid demand, *i e*, what factors initiate or stimulate intracellular proteolysis In this connection we have to keep in mind that protein synthesis in growth or repair is only one inseparable feature of the new formation of the whole protoplasm, and therefore the question raised above is intimately connected with the general problem of regulation of growth and repair There are, however, many indications that hormonal[9] and nervous factors participate in protein mobilization just as they do in fat and carbohydrate mobilization We have very little actual information about the role of nervous impulses on the deposition or mobilization of protein Trophic disturbances involving tissue proteins are frequently observed after nerve injury The role of humoral factors in the regulation of tissue protein mobilization or deposition is closely related to the general problem on the role of endocrine factors in protein metabolism and should therefore be discussed later in that connection

Catabolic Conditions —When total catabolism outweighs total anabolism, body protein is broken down in excess, therefore more N is excreted with the urine than consumed with the food which results in a negative N-balance This happens primarily whenever the *dietary protein* intake is lower than needed or the *calories* supplied with the food do not provide at least 50 to 60 per cent of the daily caloric requirement The effect of *total starvation*[96] on nitrogen excretion has been investigated several times A recent report shows that a voluntarily starving healthy woman excreted during the first few days of the starvation on the average 6 to 8 gm of nitrogen, and then in the next days, up to the twenty-sixth day 4 26 grams, and still later 2 to 3 gm daily It was also found that normally 90 per cent of the nitrogen is excreted in the form of urea but during starvation this value decreases to 54 to 69 per cent This reduction was due to an increased ammonia excretion probably the consequence of acidosis developed during starvation In the Minnesota experiments with *semi-starvation* "a progressive reduction in the negativity of the nitrogen balance" was found In patients receiving a *protein* and salt *free*,[97] but otherwise *high caloric* diet (300 gm glucose plus 150 gm arachic oil = 2,550 calories), the urinary nitrogen, the urinary ammonia, and the amino acid excretion fell from 6 8 gm total and 0 3 gm ammonia-N, at the beginning

sharply, then slowly to a minimum of 1.22 gm total nitrogen and 0.1 gm ammonias nitrogen. The progressive reduction of nitrogen excretion as seen in starvation, semi-starvation, or on protein free diets occurs not only because the easily available protein fractions of the body are progressively exhausted but probably because of an adaptation to the low food intake or low protein supply.

Apart from the cases where negative N balance develops due to inadequate caloric or N intake there are conditions in which N-excretion surpasses intake in spite of satisfactory food consumption. Such a catabolic tendency of the protein metabolism is predominant in some diseases after injuries after burns and after surgery.[98] It was found that in most of these cases the nitrogen excretion increases even when the protein and caloric intake is kept *abnormally high* or when protein hydrolysates have been provided *intravenously*. The urinary nitrogen sulphur and the nitrogen phosphorus ratios as well as the increased excretion of riboflavin indicate that it is not an inability to retain dietary nitrogen but rather an increased breakdown of tissue substance which is responsible for the highly negative nitrogen balance. The source of excreted nitrogen may vary according to the nature of the injury and the nutritional status of the afflicted person. It was found that in malnourished people or in depleted animals the loss of nitrogen after bone fracture either does not occur or is much smaller than in normals. We have to assume therefore that during the catabolic phase easily available protein depots were mobilized primarily, but it should be emphasized that in many cases the wastage of muscle protein was remarkable. The loss of body protein can be protracted, up to six weeks after injury or surgery.[99] The time at which the nitrogen excretion reaches its maximum varies it may be four to five days after injury or one to two days after surgery. The following example may show how large a quantity of tissue protein can be lost in this negative phase. In the ten days following the fracture of both legs the total nitrogen loss was found to be 137 gm. This amount represents about 7.7 per cent of the total body protein and is greater than the nitrogen content of the whole liver. Teleological reasoning may lead to the assumption that tissue catabolism in such cases has a salutory effect providing easily available building stones and energy for repair.[100] Results of experimental injuries in animals and the nature of the changes in carbohydrate metabolism which develop parallel with the nitrogen catabolism suggest a disturbance in the hormonal equilibrium as the cause of this catabolic phase. Decreased urinary excretion of sodium drop in the number of the circulating eosinophils and increased thyroid secretion indicate but do not establish satisfactorily the involvement of the hypothalamus and of the pituitary adrenal system as a direct cause of the metabolic disturbances following injury. Most of the clinically experienced authors seem to agree that due to the nature of this catabolic phase it is not advisable to enforce food intake or inject amino acids immediately after surgery.[101] Thus for instance only 2 out of 37 patients who had received a diet containing up to 130 gm protein and 2,100 calories per day could be brought in positive N-balance.

The human body normally has enough available protein and caloric reserves to subsist for a few days without intake of dietary proteins. In

order to build up such reserves in chronically sick people, it is important to improve the nutritional status whenever possible *before* surgery. It was also shown that the healing tendency is not appreciably altered by early feeding or injection of nitrogen sources. After the "catabolic phase" the improvement of appetite and consumption of palatable nutritious food, containing about 20 to 25 per cent of good protein, are important factors for early recovery.

Protein catabolism is also observed in *febrile diseases*. In fever the protein breakdown is not always directly related to the elevated body temperature or to the increased metabolic rate. It seems that in such instances the nature of the underlying disease is of importance and similar to the catabolic phase after surgery, stimulation of the hypothalamus or some endocrine organs may influence protein metabolism.

Protein Anabolic and Catabolic Effect of Hormones.—In disease or after injuries when the utilization of dietary proteins is disturbed due to the factors discussed above, it would be of eminent therapeutic importance if some methods were available which would decrease the catabolic or at least increase the anabolic processes. It has been suggested recently that certain hormonal substances with anabolic effect might be used for such purposes. This idea, along with the increasing availability of more or less pure hormone preparations, has stimulated many studies on the question of how the endocrine system influences the protein metabolism. This problem besides its biological importance, has also practical significance.

The earliest investigations in this direction are related to the effect of the *thyroid*. It was shown that injection of thyroxine increases the nitrogen excretion, however, this effect seems to be mainly the consequence of an increased basal metabolic rate and occurs even in animals whose protein reserve has been depleted by a non-protein diet consumed during the previous thirty days. The catabolic effect is not specific for the thyroid because under other conditions administration of thyroid hormone may produce anabolic effects.[102] So, for instance, in thyroidectomized animals or in severe hypothyroid conditions in children, thyroid hormone injections usually induce growth accompanied by a positive nitrogen balance. One possible mechanism for thyroid action has been suggested on the basis of experiments with N^{15} labeled glycine. This hypothesis argues that small doses of thyroxine accelerate the breakdown of tissue proteins and, at the same time, reduce the rate of amino acid catabolism.[103] Before such conclusions could be accepted, it would have to be demonstrated that the same thyroid effects hold true for several other amino acids. This is especially important since glycine has certain highly specific metabolic fates, *e.g.*, participation in creatine and uric acid formation, and hence is hardly a suitable prototype for amino acids in general.

The explanation of the thyroid effect is further complicated by the fact that during accumulation of myxedema in hypothyroidism considerable amounts of nitrogen are retained. This edema formation can be effectively counteracted by thyroxine administration. We do not yet know much about the nature of the products which are formed from the retained nitrogen in myxedema. *Byrom*[104] assumes that the thyroid favors an adult type of a relatively protein free extra cellular fluid and that in myxedema an

"infantile or atavistic" extra cellular fluid containing a high protein concentration develops. This assumption is further supported by the investigations of *Thompson*[10] who found that in myxedematous patients the concentration of proteins in the cerebro spinal fluid is abnormally high and is decreased by thyroid treatment. In hyperthyroidism the protein content of the liquor is accordingly low and increases with appropriate therapy.

Insulin, the pancreas hormone, affects protein metabolism mainly through its action on carbohydrate metabolism. In diabetes the increased glyconeogenesis involves catabolic breakdown of body proteins and as a consequence of the abnormal sugar utilization the protein synthesis is also disturbed. The protein 'anabolic' or 'negative catabolic' effect of insulin administration in diabetes is therefore evidently a consequence of improved carbohydrate utilization and of decreased glyconeogenesis. It was also observed that after insulin injection the blood amino acid concentration decreases. Furthermore, it was found that insulin increased the amino acid uptake by the isolated tissues and organs of diabetic animals. These observations do not seem to necessitate, however, the assumption that insulin has a specific effect on protein metabolism itself.[106] Recent investigations indicate that insulin may directly facilitate protein synthesis by promoting the entry of amino acids into the cells.[106a]

The observation of Long, Katzin and Fry that *adrenal cortical extracts* increase urinary nitrogen excretion has been confirmed not only in animal experiments but also in man. Similar observations have been made after injection of cortisone and of ACTH. In best agreement with these results it was found that the loss of cortical secretion results in a decreased urinary nitrogen output.[107] Based on such results, cortisone and ACTH have recently been designated as 'protein *catabolic* hormones."

The experiments in which the uptake of some labeled amino acids has been investigated did not contribute much to the understanding of the mechanism by which these hormones induce their catabolic effect on protein metabolism.[108–110]

Besides the 'catabolic,' also some 'anti-anabolic' effects of cortex hormones have been demonstrated. Thus for instance the production of connective tissue in wound healing was found to be decreased after injection of ACTH or cortisone.

According to some authors the adrenal hormones may exert many of their effects on protein and amino acid metabolism indirectly by influencing primarily the carbohydrate metabolism. This view is supported by the finding that the negative nitrogen balance seen after injection of cortex extracts, cortisone or ACTH can be often counteracted by increased food intake alone. Finally, we have to consider that the adrenal cortex produces many different hormones which may differ in their effect on protein metabolism. The classification of the adrenal hormones into 'catabolic" and 'anabolic' groups represents a rather ingenious attempt to introduce some system into this confused picture. There is no doubt, however, that all these classifications show, in Albright's expression, 'a goodly sprinkling of metaphysics.'[111]

The *pituitary growth hormone* seems to increase protein anabolism as a corollary of growth, *i.e.*, of new tissue formation.[112]

In support of this assumption increased protein synthesis and decreased amino acid catabolism have been observed in animals after growth hormone treatment. It has been also reported that in human gigantism or in active acromegaly—both conditions resulting from excessive growth hormone production—usually abnormally high amounts of nitrogen are retained.[113,114]

Some experiments suggest, however, that the effects of the somatotropic hormone on growth and nitrogen-retention are not always closely correlated. The experiments of Li indicate, for instance, that the nitrogen retained after administration of growth hormone may not be involved in permanent growth, because after discontinuing the hormone injections a large part of the retained nitrogen is soon eliminated. It was furthermore demonstrated that growth hormone injection induces nitrogen retention even when the animals are fed such incomplete protein mixtures which would not promote growth normally.[115] It was found that the nitrogen retention on zein diets, after injection of growth hormone, was the same whether the diet was supplemented with the missing amino acids or not.

All these results raise the question whether the growth hormone preparations presently available actually increase protein synthesis or whether they merely lead to an enigmatic temporary retention of dietary nitrogen.

Testosterone and some other *androgens* are, according to several authors, particularly potent protein-anabolic hormones.[116]

The nitrogen retaining effect of androgens in castrated animals is well established. It is less conspicuous in normal rats, in which it "wears off" after a short time, in spite of continued hormone treatment. No anabolic effect of injected testosterone could be demonstrated in normal sheep, pigs or pullets.[117]

In man an anabolic effect has been observed in cases of hypogonadism, male climacterium and also in children before puberty. The anabolic effect of testosterone treatment observed in some diseases seems to be the result of re-establishment of the normal hormone level in such cases where the male hormone production is decreased or where the hormonal balance is disturbed, *e.g.*, in some liver diseases.

Increased protein synthesis and decreased amino acid metabolism have been made responsible for the net decrease in nitrogen excretion.[118] The assumption that the increased nitrogen retention represents an anabolic effect, *i.e.*, formation of new body protein is, however, based mainly on circumstantial evidence.*

Albright tried to establish a correlation between nitrogen retention and increase in body weight. But such correlation was found in animals only for the first few days of nitrogen retention, then the body weight showed a "wearing off" effect. But even in such cases testosterone does not seem to have a general anabolic effect: it particularly influences as could be expected the growth of the accessory sexual tissues which accounts for about 50 per cent of the weight increase.

Another argument to prove that the nitrogen retained after testosterone is actually used for body protein synthesis was that the ratio of retained nitrogen to the retained potassium was similar to the ratio present in normal

* In animal experiments testosterone treatment increased the N retention even when the diet contained zein or gelatin as the only N sources, *i.e.* deficient proteins which cannot support protein synthesis.[118a]

muscle tissue, *i e*, 2 5 to 3 5 This argument however, does not agree too well with actual observations in convalescent surgical patients who retain potassium at a ratio of 5 mEq upwards per gram nitrogen

A further important factor to be considered is that testosterone injection often leads to retention of large amounts of water which results in more substantial increases of body weight than calculated from the N retention In normal young men on restricted sodium intake it was found that the net weight gain and water retention during the first few days following testosterone administration were out of proportion to the relatively small amount of nitrogen retention The ratio of potassium to nitrogen retained was also considerably higher than that found in normal adult tissue After testosterone was withdrawn all subjects lost weight and water, despite the fact that the net nitrogen balance remained positive for a few days[119]

All these considerations show that the theoretical foundations for the *therapeutic* use of testosterone as a *protein anabolic agent* are not firm Several authors state that in some diseases and after injury or surgery the catabolic tendency can be reversed by testosterone administration Others however found that the positive nitrogen balance can be achieved more effectively with high dietary protein than with testosterone Clinical investigations also indicate that the effect of testosterone on *real* protein synthesis is at least dubious and besides the therapeutic value of retention of a few grams of nitrogen per day as indicated in some clinical trials is at least questionable The present state of the whole problem may well be characterized by the statement of Moore and Ball[10] that more data are needed before we can find a solid place in surgical treatment for testosterone

On the protein metabolic effect of some other hormones, *e g* the estrogens even less information is available and therefore they shall not be discussed in the present survey

This short review indicates that many of the interesting findings related to the effect of the hormones cannot as yet be organized into a coherent picture All results available indicate that there is no hormone produced in the body which would specifically affect protein metabolism as, for instance, insulin or adrenalin influences carbohydrate metabolism Most of the effects which have been so far demonstrated seem to be secondary to changes in the metabolic rate, in the 'growth or repair tendency' of tissues, secondary to changes in glyconeogenesis or in sugar utilization In this connection we have to consider also the possibility that the primary effect of hormone administration on protein metabolism in some cases may be masked by regulative processes which are set to work in order to re-establish the disturbed hormonal equilibrium '

It seems furthermore that in spite of valuable information available on the metabolic action of some hormones the question as to whether their effect is of protein *catabolic* or *anti anabolic* nature is at the present state of our knowledge primarily of dialectic interest

THE ROLE OF PROTEIN DEFICIENCY IN MALNUTRITION

Insufficient intake of proteins or consumption of foods containing proteins which fail to provide the necessary amino acids are probabl

important factors in the development of human malnutrition Protein deficiency as a causative factor in human malnutrition was demonstrated by the investigations of McCay, McCarrison,[6] Boyd Orr and Aykroyd[44] Experiences collected in German and in Japanese concentration and war prisoner camps, the famous Minnesota experiments on human malnutrition and the clinical studies on pellagra and Kwashiorkor have all supplied important contributions to the understanding of protein malnutrition[122]

The effect of dietary protein deficiency has been studied in numerous animal experiments These assays have shown, that insufficient protein intake damages growth, development and health Nearly all vital processes are affected and the symptoms vary according to the severity and duration of the deficiency Feeding of *incomplete* proteins frequently leads to more serious damages than feeding of diets which contain no amino acids or proteins at all, indicating the deleterious effect of "amino acid imbalance"

The specific sequela of individual amino acid deficiencies have also been studied in animals These investigations show, *e g*, that in rats lack of arginine leads to azoospermia, insufficient methionine intake damages the liver, lack of tryptophan and some other essential amino acids leads to cataract formation Deficiency of individual essential amino acids may also change the size and the function of some endocrine organs[123] Continuation and further analysis of this line of research may lead to important findings on the biological importance of the single amino acids, it may facilitate our understanding of the phenomenon called "amino acid imbalance,' but it does not yet offer much toward the understanding of human malnutrition which presents itself in the form of *many* diseases producing quite *different* symptoms This is because human malnutrition is only rarely the consequence of pure amino acid deficiency, but mostly it results from protein malnutrition complicated either by low caloric intake or by the lack of such essential nutrients as vitamins and/or minerals

Because of the participation of protein in nearly all life processes the general symptoms of protein deficiency in man are usually quite varied and not characteristic Early symptoms of protein deficiency are, loss of weight, stunted growth, fatigue, lack of energy, irritability, changes of temperament, decreased resistance to various damaging factors, retarded wound healing and protracted convalescence Damages regarded by several authors as more specific consequences of protein deficiencies are, liver insufficiency, hypoproteinemia, nutritional edema and decreased resistance to infection due to impaired antibody formation The symptoms, when developed in adults, usually can be reversed by "dietary rehabilitation," *i e*, by feeding palatable, high grade, mixed food The fast growing, developing organism during fetal life during infancy, or during early childhood is far more susceptible to lasting damages due to protein deficiency Maternal malnutrition during pregnancy or lactation or deficient protein intake after weaning may produce permanent stigmata Damages due to malnutrition during the early stage of development seem to be responsible for certain malformations and some chronic degenerative diseases which may become conspicuous only later in life[124]

Insufficient amino acid supply in experimental animals leads to rapid decrease of *liver* protein, parallel with this the resistance of the liver to toxic injuries decreases and fatty livers may develop[125] According to recent reports, even primary liver cancer may be produced in rats by deficient diets[126] In spite of these experiments on animals the role of protein deficiency in the pathogenesis of cirrhosis, primary cancer or necrosis of the human liver is still quite obscure The important investigations of the Gilmans demonstrated that in the malnourished *Bantus*, pellagra is usually accompanied by severe damage to the liver These observations fail to indicate clearly, however, whether protein deficiency or some other nutritional factor is responsible for these hepatic changes[127]

Studies of the enzyme systems of the liver in nutritional disturbances seem to be an important new field for research in liver pathology It was found in the course of these studies that in protein deficiency the oxidase, catalase, phosphatase, arginase and cathepsin activity of the liver is de- creased[128] These investigations may open new vistas to our understandin the causal connections between protein malnutrition and clinical live disease

Connected with nutritional liver damage but not a necessary consequence of it, is *hypoproteinemia* The total quantity of circulating plasma proteins usually decreases in protein deficiency A corresponding constriction of the total circulating plasma volume, however may often mask the hypoproteinemia which may not be recognized if only the changes in plasma protein concentration are investigated The different protein fractions do not participate equally in the loss of total plasma protein the albumin decreases much faster than the globulin, probably as a sign of early liver damage

It was generally assumed earlier that hypoproteinemia develops in malnutrition because there are not enough amino acids available for satisfactory plasma protein synthesis A review of the more recent pertinent literature however supports the contention that hypoproteinemia in malnutrition represents primarily a defect of the regulation which maintains the plasma proteins at physiological levels Attributing it to a single factor, *viz* the lack of available essential amino acids does not facilitate the understanding of this basic disturbance It is also more and more evident that there is not such a close connection between loss of body proteins and development of hypoproteinemia as was assumed earlier During rehabilitation plasma proteins are resynthesized preferentially and their production may start at the time when the nitrogen equilibrium is still negative

Another symptom which may develop during protein deficiency is *anemia* Experiments on animals and clinical investigations indicate that the body protects the amount of circulating hemoglobin even more carefully than that of the other plasma proteins Hemoglobin may therefore be regenerated even during the development of hypoproteinemia[129]

A much discussed symptom of human malnutrition is *edema* formation[130] It was assumed for many decades that edema in starvation is the direct consequence of decreased intravascular osmotic pressure which develops when the plasma albumin concentration decreases Recent investigations

showed however, that there is no lower limit of blood protein concentration at which necessarily edema has to develop The extension of the sodium space, the increase of the extra-cellular fluid with appearance of pitting edema, seem to be a consequence of disturbances in the regulation of water balance Altered hormonal functions, *e g*, production of antidiuretic substances, seem to be the causative factors in emergence of edema, and not only the disturbance of intra- or extra-vascular osmotic equilibrium as was assumed earlier on the basis of Starling's classic investigations

Decreased resistance to infectious diseases as a consequence of famine and malnutrition has been observed by several authors The results of the animal experiments of Cannon and collaborators lead to the assumption that protein deficiency which interferes with the normal production of antibodies may be the direct cause for this decreased resistance The data of these authors have been confirmed by experiments in guinea pigs and rabbits where restricted feeding depressed the serological responses to antigenic stimuli Some authors, however, were not able to support Cannon's contention because they found no difference in immune responses to bacterial infection and in secondary antigenic stimulation between normal and protein starved rats [131]

Experiences in man lead similarly to equivocal results Some authors found that diphtheria antibody formation was normal in people who lost as much as 40 per cent of their weight by malnutrition [13] In "Studies of Undernutrition" in Wuppertal the response of a group of 57 undernourished persons to antigenic stimuli proved to be significantly less than that of a normal control group of 16 subjects It should be emphasized, however, that "no correlation has been found between immune response and weight loss or the level of serum proteins "[133] Grafe[134] reported that in Germany during the famine period following World War II, the incidence of infectious diseases increased only slightly, but a particular increase in tuberculosis has been observed The author expressed the opinion, however, that it was not the protein deficiency but the lack of essential fatty acids in the restricted German diet which was the responsible factor All these observations indicate that protein deficiency may interfere with optimal production of antibodies, but also show that in protein deficiency the body utilizes available amino acids preferentially for antibody synthesis This investigation further suggests that besides amino acid deficiency, the lack of some other factors such as vitamins, essential fatty acids and others may be responsible for the decreased immune-biological reaction in malnutrition

A remarkable but still insufficiently studied late effect of protracted malnutrition is the "lipophile dystrophy" (Bansi) [135] This disturbance was observed in the early phases of rehabilitation during which no N was retained in spite of satisfactory protein and caloric intake This disturbance is different from that observed during the "catabolic phase" following injury, because in "lipophile dystrophy" large amounts of fat are accumulated due to positive caloric balance and only the N-retention, the protein synthesis, is disturbed It seems that damage to the endocrine system suffered during malnutrition may be responsible for this syndrome

It was stated by Osborne and Mendel[136] about forty years ago that "the

tissues either form a typical protoplasmic product or none at all This observation has since been confirmed repeatedly It was found that in absence of some amino acids no incomplete proteins—those missing some building stones—are formed, but protein synthesis ceases completely

The somewhat dogmatic statement made by these masters of nutritional science is, however, valid for *physiological* conditions only Modern analytical methods lead to the discovery that abnormal proteins may be formed in the tissues under pathological conditions Such are the hemoglobin formed in sickle cell anemia[137] or cases of paraproteinemia, where abnormal proteins are found in the blood plasma [138]

These important recent results open an entirely new field not only in the biochemistry of proteins but also in chemical pathology

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Chapter 7

The Role of Carbohydrates in the Diet

By Samuel Soskin and R Levine

The importance of carbohydrate in human nutrition has varied greatly at different times and in different parts of the world (Grains, fruits, and vegetables are the natural foods high in it, meat, fish, and dairy products those relatively poor in it) Before the development of the modern food processing and distributing industry (and at present, in those parts of the world which have not undergone that development), the proportion of carbohydrate in the diet of any region was largely governed by the local flora and fauna Even now the proportionate intake of carbohydrate is high in tropical countries, where vegetation is luxurious and the climate leads to rapid spoilage of meat products On the other hand, the inhabitants of the Far North have always lived on a diet consisting chiefly of meat and fish Adequate nutrition is possible at both dietary extremes, if the need for calories, essential food factors, vitamins, and minerals is met [1,2,3,4]

Though there has been some change during the past fifty years in the food sources from which the carbohydrates are derived, the proportion of carbohydrate in the dietary of the United States has remained about 50 per cent of the total caloric intake Since certain foods high in carbohydrate content are relatively inexpensive, the proportion of carbohydrate in the diet has been greater at lower economic levels than in the more prosperous groups of the population The poorer nutritional status of the lowest in*come groups, however, is not so much a reflection of their high carbohydrate* intake as it is a result of the particular foods from which they derive their carbohydrates The highly refined grains and sugars, developed commercially largely because of their resistance to spoilage, are the cheapest sources of calories generally available But they have been deprived of most of the protective elements with which they are naturally endowed, hence a *casually selected* high-carbohydrate diet is likely to be poor in the essential amino acids, vitamins, and minerals [5]

THE CARBOHYDRATES IN FOODS

The carbohydrates in the ordinary American diet, the food sources from which they are derived, and the quantitative importance of each in the total intake are indicated in Table 13

DIGESTION AND ABSORPTION OF CARBOHYDRATES

Digestion [7]—The digestion of carbohydrates starts in the oral cavity Here the secretion of the parotid gland, which contains an amylase called

ptyalin, is mixed with the food and begins the conversion of starch, glycogen and dextrins into maltose. This digestion continues in the stomach until the hydrochloric acid secreted there destroys the amylase activity and substitutes acid hydrolysis for enzymatic splitting. If continued long enough, the acid hydrolysis can reduce all the digestible carbohydrates to the monosaccharide stage. The stomach usually empties itself, however, before this can occur, the digestion of carbohydrate is then taken up by the

TABLE 13.—TYPES AND SOURCES OF CARBOHYDRATES IN THE AMERICAN DIETARY (FOOD AND LIFE YEARBOOK OF AGRICULTURE[6])

Carbohydrates	**Approx. % of Total CHO Intake*	*Chief Food Source*	*End Products of Digestion*	*Remarks*
Polysaccharides				
(a) *Indigestible*				
1 Celluloses and Hemicelluloses	3	Stalks and leaves of vegetables, outer covering of seeds	0	May be partially split to glucose by bacterial action in large bowel
2 Pectins		Fruits	0	
(b) *Partially digestible*				
1 Inulin	2	Jerusalem artichokes, onions, garlic	Fructose	Chemical hydrolysis yields galactose and arabinose. Digestion incomplete; further splitting by bacteria may occur in large bowel
2 Galactogens		Snails	Galactose	
3 Mannosans		Legumes	Mannose	
4 Raffinose		Sugar beets	Glucose, Fructose and Galactose	
5 Pentosans		Fruits and gums	Pentoses	
(c) *Digestible*				
1 Starch and Dextrins	50	Grains, vegetables (especially tubers and legumes)	Glucose	The most important group quantitatively. Usually accompanied by some maltose
2 Glycogen	negligible	Meat products and sea food	Glucose	
Disaccharides				
Sucrose	25	Cane and beet sugars, molasses, maple syrup	Glucose and Fructose	
Lactose	10	Milk and milk products	Glucose and Galactose	
Maltose	negligible	Malt products	Glucose	
Monosaccharides				
(a) *Hexoses*				
Glucose	5	Fruits, honey, corn syrup	Glucose	In fruits and vegetables the contents of glucose and fructose depend on species, ripeness and state of preservation
Fructose	5	Fruits, honey	Fructose	
Galactose	0	0	Galactose	These monosaccharides do not occur in free form in foods (see under lactose and mannosans)
Mannose	0	0	Mannose	
(b) *Pentoses*				
1 Ribose	0	0	Ribose	These monosaccharides do not occur in free form in food. They are derived from pentosans of fruits and from the nucleic acids of meat products and sea food
2 Xylose	0	0	Xylose	
3 Arabinose	0	0	Arabinose	

* Calculated from the average dietary of the middle income group in the United States

enzymes of the small intestine, which operate in the more alkaline medium which prevails there. The enzymes in the small intestine are an amylase secreted by the pancreas and an amylase, a maltase, an invertase and a lactase secreted by the wall of the small bowel. All these enzymes are capable of reducing the particular sugars which they attack to the monosaccharide stage.

We have accounted for the digestion of starch, dextrins, glycogen and the disaccharides. Sugars ingested as monosaccharides do not require digestion. All the remaining carbohydrates pass through the stomach and small

intestine unchanged In the large bowel, they are subjected to the enzymatic influence of the profuse bacterial flora normal there and may to some extent be broken down to monosaccharides It is possible that minor amounts of carbohydrate are made available in this manner for absorption into the blood stream (see Fig 8)

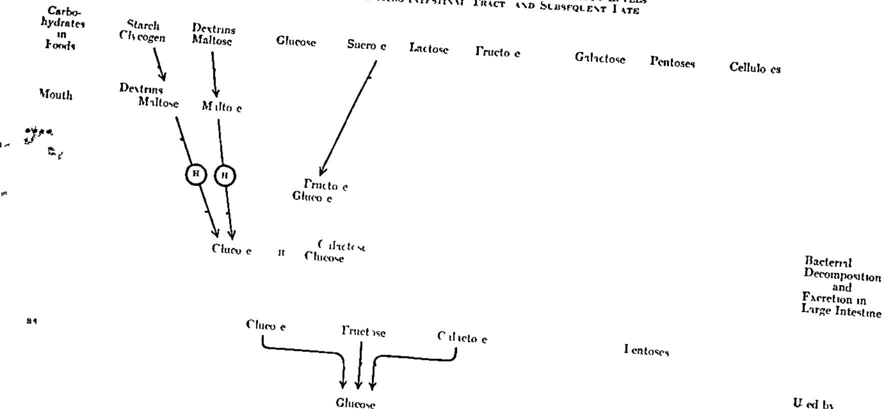
Absorption —The monosaccharides ingested as such or arising from the digestion of carbohydrates are almost completely absorbed in the small intestine Small amounts may be absorbed from the stomach It is also possible to show that when solutions of monosaccharides are introduced into the large bowel for experimental or therapeutic purposes, some sugar can be absorbed from this portion of the gastro-intestinal tract [8]

Types of Absorption —Two types of absorption occur in the small intestine (1) a specific absorption of particular monosaccharides, probably involving a phosphorylation process, and (2) a nonspecific absorption of all monosaccharides by diffusion resulting from osmotic forces across the mucous membrane [9] Glucose, fructose, and galactose are absorbed by both processes Consequently, the absorption of these sugars differs in two respects from that of other sugars (1) they are absorbed more rapidly, and (2) their rates of absorption are largely independent of their concentrations in the intestine [10] The mechanism of sugar transfer across the epithelial cell of the intestine is unknown The present evidence points against a phosphorylation process The specificity of the actively absorbed sugars differs from that of the enzyme system, hexokinase, which would be involved in phosphorylation [10a] Glucose is for the most part absorbed as such into the portal circulation, although a significant proportion may be degraded to lactic acid in the intestinal epithelium and may enter the blood in that form [10b] Fructose is transferred unchanged to the extent of about 50 per cent, some is transformed to glucose and another portion to lactic acid [10c]

Rate of Absorption of Monosaccharides —The actual rates of absorption of the three common monosaccharides vary widely, but all are much higher than the absorption rates of such monosaccharides as mannose or the pentoses, which are handled by diffusion alone It has been shown in rats, for example, that if the rate for glucose is represented as 100, that for galactose will be 110, for fructose 43, but for mannose and the pentoses only 9 [11] There are few reliable data on the absolute rates at which the various monosaccharides can be absorbed from the gastro-intestinal tract of the human being under normal circumstances The best available evidence, the work of Groen,[12] indicates that the rate of absorption of glucose from a 50 cm length of jejunum is about 8 0 gm per hour, that for galactose about 9 5 gm per hour, and that for fructose about 5 gm per hour These rates are for concentrations of sugar of 10 per cent and above Below 10 per cent, the rate of absorption varies directly with the concentration

Factors Influencing Absorption —From a practical standpoint, the figures quoted above may have little relation to the rate at which a monosaccharide enters the blood stream, when it is eaten as such or arises from the processes of digestion under the usual conditions of feeding In the latter case the time elapsing before it is absorbed from the gastro intestinal tract will be governed largely by (1) the rate at which it enters the small intestine and (2) the mixture of foods in the small intestine at the time of

Products of Carbohydrate Digestion at Various Levels of the Gastro-intestinal Tract and Subsequent Fate



" indicates that the same products as at the preceding level continue to appear

Fig 8

absorption The rate at which the sugar arrives at the small intestine depends largely on the motility of the stomach and the control of the duodenal sphincter, which can be affected by such various phenomena as hunger, emotion, local irritation (including that induced by condiments), and the composition and consistency of the food mass after mastication [7] The food mixture in the small intestine affects the rate of absorption by reason of the competition of the various constituents in the mixture for the absorbing surface of the mucosa and, in the case of monosaccharides specifically absorbed, by competition for the available transport systems [13]

Other factors which influence the amount of carbohydrate absorbed in a given individual at a particular time are (1) the normality of the mucous membrane of the small intestine and the length of time during which the carbohydrate is in contact with it, (2) endocrine function particularly that of the anterior pituitary gland,[14] the thyroid,[14] and the adrenal cortex,[15] and (3) the adequacy of vitamin intake, especially that of the B complex [16]

Since the absorption of the important end products of carbohydrate digestion requires chemical activity by the mucous membrane, it is obvious that any abnormality of the mucosal cells might interfere with carbohydrate absorption Enteritis (inflammation) is a not uncommon disturbance of this kind Celiac disease[17] may represent a more obscure disturbance of a similar nature Even when the mucosa is normal, however, an excessive rate of movement of the carbohydrate along the gastro-intestinal tract accompanying diarrheas of various origins may hurry a portion of the ingested carbohydrate into the large bowel before it can be absorbed

Normal absorption of carbohydrate does not occur if there is an anterior pituitary deficiency This probably depends for the most part upon the secondary hypofunction of the thyroid gland, for the same result may be obtained after removal of the thyroid gland when the hypophysis is intact Furthermore, the defect in absorption accompanying hypopituitarism may be relieved by the administration of thyroid extract [14] Indeed Althausen and his co-workers[18] have attempted to make use of this phenomenon as a clinical test of the state of activity of the thyroid gland They administer a standard amount of galactose by mouth, follow the rise of galactose concentration in the blood, and use the rate of the latter as a criterion of thyroid function

The adrenal cortex influences carbohydrate absorption through its regulation of the sodium chloride exchange in the body The absorption of carbohydrate from the intestine is subnormal in adrenal cortical deficiency, but can be restored to normal without the use of adrenal cortical extracts if the sodium chloride of the blood is raised to normal levels by adequate salt intake [15]

Insulin, which has such an important influence on other aspects of carbohydrate metabolism, is without apparent effect upon the absorptive capacity of the intestinal mucous membrane

THE DISTRIBUTION OF CARBOHYDRATE IN THE BODY ITS FUNCTIONS AND USES

In order to understand the distribution of carbohydrate in the body and appreciate its particular functions and uses, it is necessary first to consider

the relation of carbohydrate metabolism to that of the other two major foodstuffs, fat and protein

Carbohydrates, Proteins and Fats —Protein constitutes 75 per cent of the dry weight of the soft tissues of the body [19] In view of recent knowledge as to the protein nature of the tissue enzymes, it is a fair generalization to say that the proteins together with the hormones vitamins, and minerals constitute the metabolic machinery of the body In emergencies a certain amount of the protein machinery can be broken down and converted into fuel The amount of body protein available for this purpose at any one time however, is strictly limited as is also the period of survival possible when the body has exhausted its fat stores and is forced to depend upon endogenous protein alone [20]

Fat differs from protein in that it can be stored in practically unlimited quantities It is deposited chiefly within layers of connective tissue and does not become an integral part of the working organs of the body When food intake is inadequate to supply the caloric needs of the organism sufficient fat is mobilized to make up the caloric deficit In this way, practically the entire fat store of the body can be depleted without detriment to health Whatever harm accompanies extreme emaciation can be explained by specific deficiencies in the protective food factors incidental to the general restriction in food intake and by the loss of certain secondary structural functions of fat having to do with heat insulation and the architectural cushioning of organs Fat is, therefore primarily a fuel storage material When food is ingested in excess of caloric expenditure (whether taken in the form of carbohydrate protein or fat), the equivalent of the excess calories is deposited as fat in the adipose tissues

Carbohydrate resembles fat in that it is a fuel material but differs from it in that it is an indispensable one The tissues of the body constantly require and use carbohydrate under all physiologic conditions [21] Even a temporary fall in the blood sugar below certain critical levels is accompanied by serious disability Nevertheless, the amount of carbohydrate in the body at any one time is very small This amount if it were not replaced as used would sustain *life for only a fraction of one day* Table 14 compares the total effective carbohydrate content of a hypothetical average normal man with his caloric requirement

TABLE 14 —CALORIC EQUIVALENT OF CARBOHYDRATE CONTENT OF NORMAL MAN

Body Weight 70 kg Liver Weight 1800 gm Muscle Mass 35 kg Volume of Blood and Extracellular Fluids 21 liters

	Percentage	*Gm*
Muscle glycogen	0 70	245
Liver glycogen	6 00	108
Blood and extracellular fluid sugar	0 08	17
Total body carbohydrate		370 gm
Caloric equivalent (370 × 4 1)		1517 calories
Caloric requirement (Sedentary occupation)		2800 calories per 24 hours or 116 7 calories per hour

Total body carbohydrate could supply caloric needs for $\left(\frac{1517}{116\ 7}\right)$ 13 hours

From this it is clear that unless large amounts of carbohydrate are regularly ingested, the carbohydrate needs of the body must be met by the conversion of the other foodstuffs into carbohydrate. It is the active fuel of the body; it is stored only in small quantities and is taken in or made as required.

Carbohydrate Distribution.—The carbohydrate of the body is largely present in the form of glycogen in the skeletal, cardiac, and smooth muscles. In these motor tissues it serves as an emergency reserve of fuel which can be mobilized more rapidly than glucose can reach them through the regular channels. Most of the remaining carbohydrate in the body is found in the manufacturing and distributing system, namely, in the liver as glycogen and in the blood and extracellular fluids as glucose. Relatively small amounts of glycogen, however, are also found in practically all other organs and tissues of the body.

The reason the greater part of the body carbohydrate is present as glycogen (the polymerized storage form of glucose) is that all the hexoses which result from the digestion of carbohydrate in the intestine, and are absorbed into the blood stream, are converted into glucose. This occurs largely, but perhaps not entirely, in the liver.[13, 27, 3] Similarly, in the post-absorptive state or during fasting, when the liver must supply sugar to the blood from the body's own resources, glucose is the carbohydrate it manufactures from protein and fat. Nevertheless, there are minor amounts of other forms of carbohydrate in most tissues and organs. Among these are special-purpose carbohydrates, carbohydrates presumably not used as fuel, for example, the galactose in the galactolipins of nervous tissues,[24] the pentoses associated with the nucleoproteins, and the glucose of the widely distributed glucoproteins.[5] And during lactation, lactose is made in the breast and is present in the secreted milk. Finally, there are a number of such degradation products of glucose as the hexose and triose phosphates,[8] which are caught in transit as the glucose is utilized.

Table 15 summarizes the distribution of the quantitatively important forms of carbohydrate in man and in certain laboratory animals. To some extent, we must rely on the data obtained from experiments with animals

TABLE 15.—THE DISTRIBUTION OF CARBOHYDRATE IN VARIOUS TISSUES OF RAT, DOG AND MAN*

Tissue	*Rat*		*Dog*		*Man*	
	Glycogen, Percentage	*Glucose, Mg Per centage*	*Glycogen Percentage*	*Glucose, Mg Per centage*	*Glycogen, Percentage*	*Glucose Mg Per centage*
Skeletal muscle	0.81–1.06[7]	50–70	0.55[29]	40–60	0.4–0.6[30]	
Liver	2.5–8.3[27]		6.10[29]		1.5–6.0[31]	
Heart	0.3–0.6[9]		0.47[29]			
Kidney			0.15[29]		0.4[31]	
Brain	0.08[29]		0.1[28]	57[28]		
Skin		77[32]	0.08[32]	71[32]	0.08[32]	60–82[32]
Blood and Extra cellular Fluids		90–120[27]		60–80		60–90

* The figures represent ranges found on a mixed diet.

to interpret the relatively meager data available for human beings This is because both glucose and glycogen (especially the latter) are labile substances when present in the tissues, and few opportunities to obtain human tissues under the proper conditions for accurate analysis present themselves However, the close agreement of the reliable data which we do have for human-beings with those obtained from experiments with animals increases their significance

The Fuel of Muscular Exercise —*In an exhaustive review of the subject,* Gemmill[33] has aptly reviewed the situation with regard to the fuel of muscular exercise as follows

> "From the survey of the literature it is obvious that the use of carbohydrate is of primary importance as a fuel for muscular exercise in man The evidence comes from the slight increase in efficiency on a carbohydrate diet the prolongation of muscular effort when carbohydrate is ingested, the fall in blood sugar during long continued muscular exercise and the production of lactate at the beginning of exercise and during severe exercise The evidence that protein is used during exercise indicates that it is of secondary importance, probably to supply carbohydrate or carbohydrate intermediates The results of experiments on fat utilization during muscular work have demonstrated that this substance is used indirectly There is no experimental evidence at the present time for the direct utilization of fat by mammalian muscle However, the indirect utilization of protein or fat must be an efficient process since the exclusive feeding of these substances to man does not have a marked effect on muscular efficiency during short periods of exercise "

However since Gemmill's review was written evidence has been brought forward to indicate that fatty acids can be oxidized by the liverless animal[81] and by muscle extracts *in vitro* [82 83] But whether this occurs in intact muscle or to what extent it occurs in relation to the total caloric expenditure, has not been determined As a matter of fact, the work on the whole animal was done under resting conditions, so that the peripheral oxidation of fat observed may have no bearing as regards the fuel of muscular exercise Hence it is still necessary to conclude that carbohydrate is a major fuel of muscular exercise

The significance of this from the standpoint of nutrition is obvious If carbohydrate is not available as such in the diet it must, in order to satisfy the fuel requirements of the active tissues, be made by the body from those foodstuffs present in the diet The eating of adequate amounts of carbohydrate therefore spares the body the work of making its fuel As fuel carbohydrate is naturally more important when the body engages in moderate or severe muscular exertion than it is when the body is at rest The great demand for fuel accompanying muscular exercise may rapidly exhaust the carbohydrate stores This is evidenced by a decrease in the glycogen content of the liver and the muscles if the exertion is sufficiently severe and prolonged it may result in an abnormal lowering of the blood sugar level [34] These phenomena are accompanied by increased breakdown of body protein (reflected in an increased excretion of nitrogen in the urine[33]) and accelerated breakdown of body fat (reflected in a rise in the level of

ketone bodies in blood and urine)[35] When violent exercise is preceded or accompanied by a large intake of carbohydrate, the body, on the basis of calories expended per unit of oxygen intake, works somewhat more efficiently And there is a minimum *increase in nitrogen* excretion and ketone formation This effect of carbohydrate is an example of its protein-sparing and antiketogenic action

The Efficiency of Carbohydrate as a Fuel —It has just been said above that carbohydrate is a more efficient fuel for *muscular exercise than* either protein or fat This does not imply that portions of the protein or fat molecules are wasted when they are so used It means that protein and fat molecules, when used as fuel, yield less than their total caloric value in the form which can be used by muscle The remainder is used for the conversion of these molecules into suitable fuel This conversion occurs in the liver, which supplies the other organs with fuel by way of the blood stream

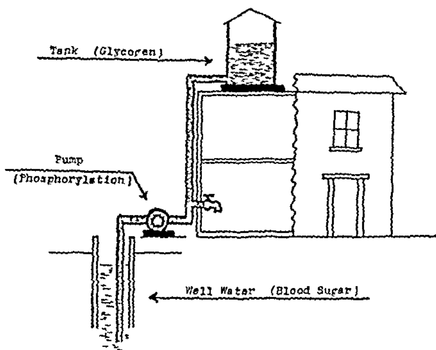


Fig 9

Since the amount of glycogen present in the muscle at any one time is sufficient for only short periods of work the carbohydrate used by the muscle must eventually come from the blood sugar The glycogen within the muscle cells may be reasonably supposed to serve best in emergencies, when the muscle is unable to draw sugar from the blood as quickly as needed But as a matter of fact glycogen is more than a conveniently packaged form of carbohydrate lying on the pantry shelf It is now known that more energy is derivable from a certain amount of glycogen than from an equivalent amount of blood sugar Since it requires a certain amount of energy to bring the blood sugar into the metabolic system of the muscle (as hexose 6-phosphate[36]), all the energy inherent in the glucose is not available for useful work On the other hand, the breakdown of glycogen to the same

stage does not require energy, hence all its inherent energy is quickly made available[36] This is not to say that one gets something for nothing from glycogen, it requires some energy to build up the glycogen in the first place But this energy is expended during a quiescent period when plenty of it is available The situation is analogous to that portrayed in Figure 9[37]

Here the water in the well represents the blood sugar, the pump stands for the phosphorylating mechanisms and the tank on the roof represents the glycogen store It is readily understandable that when the tank contains stored water, the tap can deliver a rate of flow far beyond the rate capacity of the pump The water stored during periods when the tap is closed is at a higher level than the original source of the water and therefore, stores some of the energy applied by the pump This potential energy is released when the tap is opened Too great an outflow from the tap will, of course, exhaust the stored water and reduce the rate of flow from the tap to the rate at which the pump is capable of operating A similar condition obtains in muscle when excessive rates of work over prolonged periods are attempted

The application of these physiologic facts to clinical phenomena is exemplified by the greater stores of glycogen and of phosphate esters found in the muscles of animals which have been trained to perform prolonged work[38] This probably also applies to the physical abilities of manual laborers and of athletes Conversely, the characteristically low muscle glycogen level found in poorly controlled diabetic patients and in hyperthyroid individuals is accompanied by muscular weakness

Special Functions of Carbohydrate in the Liver —In the liver aside from its use as fuel, carbohydrate has protective and detoxifying action and a regulating influence on protein and fat metabolism

The liver of a well fed normal animal contains a higher percentage of glycogen than any other of that animal s tissues It is known that such a liver is more resistant to various types of noxious agents than one which has been deprived of its glycogen by starvation or disease This has been shown in animals for such various types of poisons as carbon tetrachloride,[39] alcohol,[40] and arsenic[41] and in human beings for a variety of diseases accompanied by toxemias of bacterial origin[42 43] The defenses of the liver against toxic agents are of great importance to the body as a whole for one of the chief functions of the liver is to remove or destroy such agents (toxins) before they reach other vital tissues which are not equipped to deal with them For this reason, the maintenance of a high glycogen level in the liver is essential to the health of the whole organism

It is now known that most of the glycogen of the liver is present in the form of a complex with protein[44] It is reasonable to assume that just as the protein part of the complex stabilizes the glycogen so the glycogen will tend to protect the protein More definite knowledge is available of the role of carbohydrate in specific chemical reactions which transform certain poisons into relatively innocuous substances One such mechanism is the conjugation of glycuronic acid derived from carbohydrate with poisons which possess a phenolic hydroxyl group[45] Indeed this mechanism is one of the means by which the body regulates its steroid hormone metabolism and protects itself from the harm which might result from an excess of the sex

hormones.[46] It is also possible that the carcinogenic substances of the steroid type may be disposed of in the same manner. Another hepatic detoxifying mechanism is the acetylation of such substances as *p*-aminobenzoic acid[47] and sulfanilamide.[48] In this type of conjugation, the acetyl groups are derived from carbohydrate, probably through pyruvate and acetyl phosphate. The rates of glycuronate formation and of acetylation have been shown to depend directly upon the concentration of carbohydrate in the liver.[48,49]

The protein-sparing action of carbohydrate has already been mentioned. This action occurs partly in the liver, for that is the organ primarily responsible for the deamination of amino acids. Up to the point of deamination, the fate of amino acids in metabolism is not finally determined. They may be used as building blocks from which to form proteins for the repair or growth of tissues, or they may be broken down for use as fuel. Once deamination has occurred, the amino acids are divorced from protein metabolism. The amino group is converted to urea and excreted, the nonnitrogenous fraction is either used as a source of energy or is converted to carbohydrate or fat. The rate of deamination in the liver decreases as the available carbohydrate increases.[50] An ample supply of carbohydrate thus conserves the products of protein breakdown in a form which may be used by the body to build or maintain its own protein structure. To put it in another way, a minimal intake of protein, adequate for the body's needs when taken together with good amounts of carbohydrate, may become inadequate when the carbohydrate intake is insufficient.[51]

The availability of carbohydrate to the liver also determines how much fat will be broken down by it. There is no direct index of the rate of fat metabolism in the liver, for, unlike protein metabolism, it is not accompanied by the excretion of a characteristic end product in the urine. However, it happens that fatty acids are not completely metabolized by the liver and that the end products of fatty acid metabolism in this organ are the so-called ketone bodies, β-hydroxybutyric and acetoacetic acids.[52,53,54] These ketone bodies go to the peripheral tissues for complete oxidation. Ordinarily, the rate of fat breakdown and ketone body formation is such that the ketone bodies are promptly disposed of by the peripheral tissues. But when fatty acid breakdown becomes excessively rapid and the rate of ketone formation in the liver begins to exceed the rate of disposal by the peripheral tissues, accumulation of the ketone bodies begins to occur in the blood and excretion of them in the urine (ketosis). Under these circumstances, in an otherwise normal animal, the administration of carbohydrate causes a prompt disappearance of the ketone bodies (antiketogenic action). This effect of carbohydrate occurs partially in the liver and is due to an inhibition of the breakdown of fatty acids. Carbohydrate intake by the fat tissues themselves inhibits their output of fatty acids, which are the raw material for ketone production.[54a] Together with its protein sparing action, the antiketogenic action of carbohydrate serves to regulate the proportion of the different foodstuffs prepared by the liver for use as fuel in the peripheral tissues.

In discussing the special functions of carbohydrate in the liver, we have referred both to the glycogen content of that organ and to the "availability" of carbohydrate to it. These terms may or may not be synonymous, for it is

still not known whether sugar may be used directly by the liver cells or must first be built up to glycogen In any case, the glycogen content of the liver is a good index of the amount of carbohydrate available to the hepatic cells, and from a nutritional standpoint it is important to remember that carbohydrate is the foodstuff which leads to the highest levels of liver glycogen Fairly good glycogen stores in the liver can be obtained when protein is predominant in the diet, but a high-fat diet results in a liver poor in glycogen [7 55] The medical uses of the high carbohydrate diet or of the *intravenous administration of dextrose solution are directed towards the* protection of the liver by insuring building up rich glycogen stores [43] Protein has been used with the same ultimate purpose in mind but it is less effective, probably because its effectiveness is in proportion to its convertibility into sugar

In attempting to drive the hepatic glycogen stores upward at a maximal rate for therapeutic purposes, physicians have often attempted to reinforce the effect of high carbohydrate intake by the simultaneous administration of insulin This is not the place to discuss the physiologic action of this hormone, but it is important to note that the administration of insulin with carbohydrate to the nondiabetic organism actually results in a lower liver glycogen level than does administration of the same amount of carbohydrate without insulin [56] This is because insulin also influences the intake of glucose and the deposition of glycogen in the skeletal muscles The bulk of these muscles, much greater than that of the liver serves to draw off most of the administered carbohydrate, hence the liver is deprived of glycogen which might otherwise be deposited in it

Carbohydrate and the Heart —The previous discussion of carbohydrate as the most efficient fuel for muscular exercise and of the muscle glycogen as an important emergency source of contractile energy applies in even greater measure to cardiac muscle than it does to skeletal muscle The latter can in some measure accommodate itself to a decreased supply of carbohydrate by decreasing its work The heart cannot stop to rest A temporary reduction in the supply of sugar to the normal heart (as in induced attacks of hypoglycemia) has little apparent effect on the organ although a definite change in the electrocardiogram may be noted [57] The apparent lack of influence of hypoglycemia on the heart may be due to the normally good glycogen stores to be found there But in the heart which has been damaged by disease and in which the initial glycogen stores are poor, hypoglycemia may precipitate stenocardial symptoms with angina and even result in death This has been noted in diabetic[58] as well as in nondiabetic cardiac patients, both, it has also been observed, are likely to do better when the blood sugar is somewhat elevated, even above the normal range High-carbohydrate therapy has been successfully used on this basis [59] The cardiac glycogen level is regulated in part by the "growth' hormone of the pituitary Because of this influence cardiac glycogen rises during fasting and after pancreatectomy or phlorhizination [59]

The Indispensability of Carbohydrate to the Central Nervous System — Of all the organs and tissues in the body, the central nervous system is most dependent upon the minute by minute supply of glucose from the blood In the discussion of carbohydrate as fuel for muscular exercise it was stated

that carbohydrate could be used directly, protein and fat only indirectly. With regard to the central nervous system, it has been well established that carbohydrate is the principal fuel.[60, 61] And the need of nerve tissue for glucose is even more specific than this statement would indicate. It is true that when slices of brain tissue are studied *in vitro* with regard to their ability to maintain respiration at the expense of various substrates, it is discovered that a number of degradation products of glucose will serve as well or better than glucose.[60] But, none of these intermediates have been shown to have any ameliorating effect upon the hypoglycemic symptoms caused by lowering the blood sugar level *in vivo*.[6] In other words, glucose as such has a specific influence and is indispensable for the maintenance of the functional integrity of the nerve tissue. When the level of blood sugar is lowered in a living organism, tissues having ample stores of glycogen may use these to tide them over the lean period. Nervous tissue has little glycogen and it is doubtful whether that little can be mobilized for use in emergencies. The glycogen content of nervous tissue remains more or less constant under most conditions, including hyperglycemia and hypoglycemia, and may be largely an integral part of the nerve structure.[28] The unavailability of the glycogen present in the nerve cells for metabolic use is evidenced by the dramatically rapid development of hypoglycemic symptoms when the blood sugar level is lowered.

The susceptibility of the central nervous system to hypoglycemic shock has been utilized in the treatment of schizophrenia and other nervous disorders. The hypoglycemia has been produced by the administration of large doses of insulin, and the earlier advocates of the method spoke of the possible favorable effect of the hormone on the metabolism of the brain. It is now evident that insulin produces its results by lowering the blood sugar level as it forces the sugar into the peripheral tissues, largely the muscles. By this means the central nervous system is deprived of its indispensable substrate and suffers true shock or damage, which does not differ very much either in its mechanism or its results from the type of shock caused by asphyxia.[63] Indeed the latter, in one form or another, has also been used as a method of treatment. That the insulin shock treatment is correctly named and is not due to a favorable influence on metabolism, is also shown by the fact that prolonged hypoglycemia results in histologically demonstrable and functionally irreversible damage to brain tissue.[64]

THE RELATIONS OF CARBOHYDRATE TO OTHER NUTRIENTS IN THE BODY

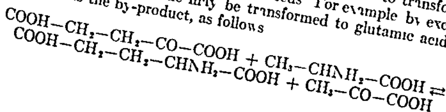
The Transformation of Carbohydrate into Fat.—In the previous discussion of fat as a fuel storage material, it was pointed out that when food in excess of caloric expenditure is ingested (whether in the form of carbohydrate, protein or fat), the equivalent of the excess calories is deposited as fat in the adipose tissues. With this in mind it is, strictly speaking, incorrect to label any of the foodstuffs as being particularly "fattening." Any one of them may be so if taken in sufficient quantities. But because of its proportion in the diet, its lower cost and its use in confections, carbohydrate is quantitatively the most important precursor of fat.

It has usually been thought that the transformation of carbohydrate into fat occurs exclusively in the liver. This is apparently not so, for using C^{14} labeled glucose, Chaikoff *et al.*[84] showed that the liverless animal could perform that transformation, although it occurred five times as rapidly in the presence of the liver. The main site is the adipose tissue itself as Wertheimer[85] and other have shown both *in vivo* and *in vitro*.

The fat which arises from carbohydrate in the body is the so called "hard" fat composed in the main of the highly saturated palmitic and stearic acids.[60] This is probably of more concern to stock raisers than to human nutritionists. The former have long known that they could control the physical qualities of the fat in meats by varying the proportions of carbohydrate and oils in the diet of their animals. Of course carbohydrate cannot be substituted completely for fat in the diet since it does not carry with it the essential fatty acids and the fat soluble vitamins which cannot be manufactured by the body.

The chemical pathway which glucose follows on its way to fat is beginning to be understood. It was long known that thiamine (vitamin B_1) was necessary for the formation of fat from carbohydrate.[66] Since thiamine is known to be a necessary coenzyme in the reactions of pyruvic acid a possible route for the initial steps of carbohydrate to fat is thus outlined. The carbohydrate is degraded to pyruvic acid which in turn forms acetyl Co A. From this point on it is possible that the further growth of the fatty acid chain occurs in a reverse manner to that which has been described for its breakdown. According to the best hypothesis the latter process involves the successive splitting off of two carbon atom fragments (as acetic acid).[5, 68] The reverse of this process in fat formation would demand the successive appearance of fatty acids composed of four, six, eight, ten, twelve, fourteen and sixteen carbon atoms. While this has not been demonstrated for adipose tissue it is suggestive that all these stages of fat formation are found in an organ which is a very active fat builder, namely, the lactating breast.[69]

Carbohydrate and Protein Metabolism.—Earlier writers on metabolism have talked somewhat loosely of the formation of protein from carbohydrate. Strictly speaking such a transformation is impossible for the amino groups which characterize the building stones of proteins must be derived from amino acids or proteins ingested as such. What can and does occur is the exchange of the amino group of an amino acid with the keto group of a keto acid derived from carbohydrate, a process known as transamination.[70, 71] In this process the carbon residue of the amino acid reverts to a carbohydrate intermediate so that there is not any quantitative increase in the amount of protein precursor resulting from the reaction. What the body gains from the interchange is the ability to transform an amino acid it has in excess into another it needs. For example by exchange with α-ketoglutarate alanine may be transformed to glutamic acid with pyruvic acid as the by-product, as follows:



$$COOH-CH_2-CH_2-CO-COOH + CH_3-CHNH_2-COOH \rightleftarrows$$
$$COOH-CH_2-CH_2-CHNH_2-COOH + CH_3-CO-COOH$$

The Vitamin B Complex in Carbohydrate Nutrition —It is known that the vitamin B complex plays an integral part in carbohydrate metabolism and that the need for this group of vitamins depends upon the amount of carbohydrate eaten Why was knowledge of its existence not acquired much earlier in human experience, and why did the race not suffer from lack of that knowledge? The answer to these questions is that it was only in comparatively recent times that the natural union between the vitamin B complex and carbohydrate, a union existing in whole grain and plants, was broken by the industrial processing of foods Before this occurred, the supply of the B vitamins was automatically adjusted to the amount of carbohydrate eaten, the occurrence of vitamin B deficiency with its consequent disturbance in nutrition is, therefore, a comparatively recent development in the Western World In the Orient, the earlier large-scale introduction of polished rice led to the first known instances of vitamin B deficiency (beriberi) and, indeed, to the first recognition of the existence of this group of vitamins [7]

The vitamins, as the name signifies, were first regarded as mysterious elements essential for life As the different vitamins were successfully recognized and extracted in concentrated form from their natural sources, experimentation with these products led to the recognition of definite clinical syndromes resulting from lack of them and cured by administration of them More recently, the actual chemical identity of many of the vitamins has been established and a number of them have been synthesized Coincidentally, the development of tissue enzyme chemistry has revealed a great deal about the chemical steps through which the foodstuffs are broken down and used for energy It is now known that each of the chemical steps is accomplished by the activity of one or more enzymes (protein catalysts) and that each of the enzymes requires one or more cofactors for its optimal activity In some instances the cofactor is a simple mineral substance like iron or magnesium or phosphorus, in others the cofactor is a more complex organic substance known as a coenzyme So far, the vitamins whose functions are known have been found to be coenzymes or to give rise to coenzymes in the body [73]

Figure 10 outlines the known steps in the breakdown of carbohydrate and indicates the points at which the various components of the vitamin B complex play an essential role The role of various minerals in carbohydrate metabolism is similarly indicated

Since the breakdown of carbohydrate is essentially similar in all tissues and organs it follows that a vitamin B deficiency will impair carbohydrate metabolism in every structure of the body The clinical syndromes which have been described are therefore, merely the most obvious manifestations, those occurring in the tissues and organs which suffer most acutely and are most easily accessible for purposes of examination Consideration of Figure 10 also shows the fallacy of regarding any single factor of the B complex as more important than another, for the normal chain of events can be broken by a lack of any one of them For this reason, and until we have isolated and known the precise function and optimal proportion of each component part of the B complex, a natural source containing all the factors remains the

best protective dietary supplement with which to avoid the evils of modern food refinement

The Utilization of Simple Sugars Other than Glucose.—In the previous section on the distribution of carbohydrate in the body it was pointed out that all the hexoses absorbed from the gastro-intestinal tract are converted into either glucose or glycogen. This conversion, which takes place largely in the liver, is ordinarily so efficient that there is little need to consider any further fate which sugars like fructose and galactose may undergo. However, under special circumstances as when the function of the liver is impaired or these sugars enter the blood in overwhelming quantities, there occur interesting anomalies of carbohydrate nutrition which deserve some brief mention. Lactose is also of interest here for during lactation it is formed in large quantities by the breast of the female at that time too it may appear in the blood and the urine. The pentoses are sometimes involved in an hereditary anomaly of metabolism.

Fructose.—Though the conversion of fructose to glucose occurs largely in the liver there is some evidence that it may take place to a smaller extent in the intestinal mucosa and the kidney.[13,23,4] The hexokinases of certain tissues (muscle brain) can catalyze the formation of fructose-6 phosphate from fructose. Other tissues (especially liver) contain a specific fructokinase which leads to the formation of fructose 1 phosphate which in turn is split to trioses. The trioses may be transformed to pyruvic and lactic acids or resynthesized to fructose diphosphate. This ester proceeds by reversal of the glycolytic steps to glycogen or to free glucose by the action of glucose 6-phosphatase.[75] The phosphorylated fructose also appears to be more readily degraded to lactic acid than is glucose 6-phosphate. Hence when fructose appears in excess in the blood it is accompanied by a rise in lactic acid.[76] Some of the latter may be converted into glucose or glycogen by the liver.

When any of the foregoing hepatic mechanisms are impaired either by liver disease or by an hereditary anomaly known as essential fructosuria, there is difficulty in disposing of the fructose taken in through the gastro intestinal tract and it accumulates as such in the blood. And since it is a substance which is not held back by the kidney as efficiently as is glucose it appears in the urine in abnormal quantities. Fructose is a reducing sugar not distinguishable from glucose by the routine chemical tests. From the medical standpoint therefore it is important not to confuse fructosuria with diabetes mellitus.

Lactose and Galactose.—Lactose is split into glucose and galactose in the process of digestion. It may therefore be considered together with the galactose ingested as such. However from a nutritional standpoint the presence of lactose in milk and milk products renders it much more important than galactose.

There is good evidence that galactose is converted to glucose by the liver by phosphorylating steps similar to those described for fructose.[7] The galactose 6-phosphate is transformed by means of the uridine-diphosphate coenzyme to glucose 6-phosphate.[77a] The congenital absence or weakening of this system is the biochemical defect in galactosemia. The lactating breast manufactures lactose and presumably has galactose avail-

POINTS OF ACTION OF VITAMINS AND MINERALS IN CARBOHYDRATE METABOLISM

(The substances required for a particular reaction are necessary in both directions of the reaction)

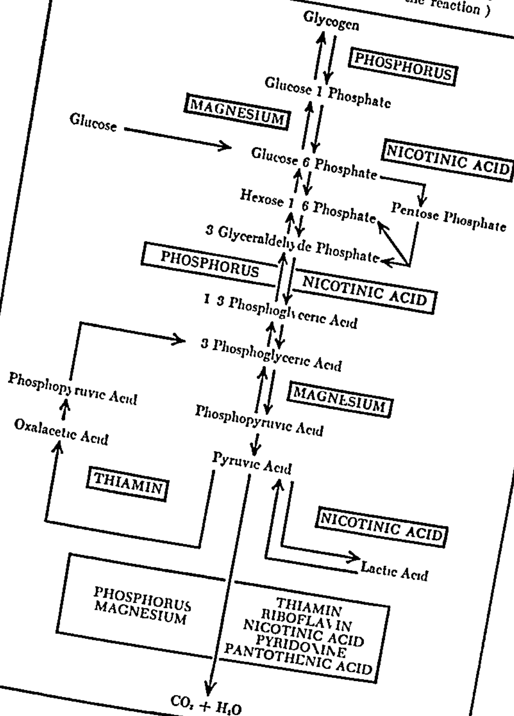


FIG 10

able for the purpose,[78] but it is not known whether all the galactose is made in the breast or whether some of it originates in the liver and is transported to the breast Since both lactose and galactose may be found in the blood and urine of lactating females the mere presence of these abnormal constituents does not give any indication of their site of origin As with fructose, it is of importance medically to distinguish between galactosuria lactosuria and glucosuria

In the previous discussion of the special functions of carbohydrate in the iver, mention was made of its protective and antiketogenic action Liver lycogen formed from ingested galactose or lactose may be more beneficial the organism than glycogen originating from other materials This is because, for some unknown reason the 'galactose glycogen is more stable It has been shown that when galactose is administered to animals together with a ketogenic agent, the ketosis which follows is less severe than that which follows similar administration of glucose or fructose

Pentoses —In contrast to the hexoses which are important energy materials the 5-carbon atom sugars are much more important as part of the machinery of the body Pentoses are incorporated in at least one vitamin (riboflavin) several tissue coenzymes (diphosphopyridine nucleotide triphosphopyridine nucleotide alloxazine adenine dinucleotide) and all the nucleoproteins However, when pentoses is such are ingested they are not utilized but are eliminated more or less quantitatively in the urine and feces It is possible that the pentoses which are eaten in combined form as part of natural food constituents (riboflavin and the nucleotides for example) do contribute to the pentose content of the tissues It is known that the body is able to synthesize pentoses for itself—from glucose by way of glucuronic acid[79] The hereditary anomaly known as essential pentosuria is as yet unexplained in detail

SUMMARY

We must take cognizance of the human failing whereby the very act of examining a subject in great detail tends to exaggerate its importance We have seen that carbohydrate not only is the primary fuel of the body but also is involved in important portions of its functional machinery The carbohydrate stores, though relatively small in comparison with those of fat, play a protective role in some of the most vital organs They may be of he utmost importance when a ready source of energy is required to enable he organism as a whole to cope with an emergency Despite all this however, the evolutionary processes have resulted in so flexible a metabolic stem that the higher mammals and man can get along very nicely when little or no carbohydrate is available Under these circumstances, the body makes its own carbohydrate fuel from noncarbohydrate materials But this is a wasteful process because some energy must be used for the conversions and then there is more wear and tear on the metabolic machinery

If, with the foregoing considerations in mind we could divorce ourselves from previous dietary experience and construct an ideal adult diet, we would choose the following (1) protein sufficient in quantity and quality to repair the protein machinery from day to day —and a little more, to be on

the safe side (and of course a sufficiency of all the vitamins and minerals), (2) enough fat to carry the essential fatty acids and fat-soluble vitamins and make it unnecessary to eat too large a bulk of other food, (3) enough carbohydrate to supply all the rest of the calories necessary to maintain weight. The diet outlined is a fair approximation of that which the human race has actually adopted on the basis of experience in those fortunate parts of the world where food resources are rich and the choice is not limited.[80]

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Chapter 8

The Absorption, Digestion, and Metabolism of Fats and of Related Lipids

By Roslyn B Alfin-Slater and Harry J Deuel, Jr *

INTRODUCTION

Fats constitute a separate category of foodstuffs which have been recognized since prehistoric times Markley[1] states that the use of fats is probably instinctive, moreover, he also indicates that the utilization of fats and waxes, as illuminants, for cosmetics, in medicaments, and as lubricants, dates back to periods before recorded history As early as 1823, Chevreul[2] established the fact that common animal and vegetable fats are composed of the alcohol, glycerol combined with various higher fatty acids

The terms, "fats" and "oils," have come to connote the same foodstuff Ordinarily, the so-called fats are solid at the usual temperatures, while oils are liquid, this is not an absolute distinguishing factor, however, as some fats may be changed to oils when maintained in a warmer environment, while some oils may solidify to fats when transferred to a colder climate Both fats and oils are glyceryl esters of fatty acids Those having lower melting points (and which are therefore more liable to remain liquid) usually have a larger proportion of unsaturated acids than do fats which have higher melting points (and which are solid at the temperature under consideration) In a few cases of natural fats, the melting point is also related to the length of the fatty acid chains, those possessing the shorter chains usually remain liquid at lower temperatures than those with longer fatty acid chains One should not confuse hydrocarbons such as mineral oils, which cannot be utilized by the animal body, with triglyceride fats Moreover, the so-called "essential oils" represent another group of compounds quite distinct from the vegetable fats, both chemically and as sources of calories

Fats and oils comprise the most important group from a quantitative standpoint, of the larger class of food components known as lipids The lipids include those substances which are insoluble in water, but which dissolve in the so-called fat solvents (diethyl ether, petroleum ether, chloroform carbon tetrachloride, hot alcohol, benzene, acetone, gasoline, and fat itself) They are related either actually or potentially to fatty acid esters and are utilizable by the animal organism Inasmuch as the members of the lipids other than triglycerides also possess most important physiologic functions, and since they are ordinarily found associated with fats and oils, it is of considerable importance to understand the nature of these compounds

* Deceased

Classification of Lipids

A convenient classification of lipids, which is an extension of that suggested by Bloor[3] and by Deuel,[4] is given below

I SIMPLE LIPIDS

1 Neutral Fats —These include glycerol esters (triglycerides) of fatty acids (chiefly oleic, stearic, palmitic and linoleic)

2 Waxes —These are esters of higher monatomic alcohols with fatty acids (similar to those in neutral fats and also having longer carbon chains)

(1) *True Waxes* —Esters of palmitic stearic oleic or other higher fatty acids with cetyl (hexadecyl) steryl (octadecyl) or other higher straight-chain alcohols of either vegetable or animal origin comprise this group

(2) *Cholesterol Esters* —These are esters of the sterol cholesterol ($C_{27}H_{45}OH$) with palmitic stearic oleic or linoleic acids

(3) *Vitamin A Esters* —Normally these are the palmitic or stearic acid esters of vitamin A The so-called colored fats which are mono or di-esters of the carotenols should be included in this category In contradistinction to the waxes these compounds are readily hydrolyzable

(4) *Vitamin D Esters* —Vitamin D ordinarily occurs as an ester

II COMPOUND OR CONJUGATE LIPIDS

1 Phospholipids (Phosphatides) —These compounds are characterized by the presence of an orthophosphate molecule as an integral part of he structure

(1) *Lecithins* —This group is composed of glycerol two fatty acids (one saturated and one unsaturated) in ester linkage phosphoric acid and choline This constitutes the most widely distributed class of phospholipids

2) *Cephalins* —These were formerly considered to consist only of lipids similar to lecithins in which ethanolamine occurred in place of choline This class is now known to consist of at least three types of compounds as follows

(*a*) Phosphatidylethanolamine This is the classical cephalin composed of glycerol, two fatty acids in ester linkage phosphoric acid and ethanolamine

(*b*) Phosphatidylserine This is similar to phosphatidylethanolamine except that the amino acid serine replaces ethanolamine It was isolated by Folch[5]

(*c*) Phosphatidylinositol (Lipositol) This contains inositol ($C_6H_{12}O_6$) fatty acids phosphoric acid ethanolamine and possibly galactose and tartaric acid in an undefined combination it has been isolated from brain[6,7] and from soybean oil[8]

(3) *Sphingomyelins* —These contain a nitrogenous base, sphingosine, a single fatty acid molecule, phosphoric acid, and choline, but no glycerol

(4) *Phosphatidic Acids* —These are compounds prepared from plant sources, similar to lecithins, but from which the choline has been removed [9] On hydrolysis they yield fatty acids (saturated and unsaturated), glycerol, phosphoric acid and calcium Hanahan and Chaikoff[10] believe that phosphatidic acid does not occur normally as a primary product but only as a result of enzyme hydrolysis of lecithins or cephalins in the course of their preparation in the laboratory

2 Cerebrosides —These compounds contain a carbohydrate molecule as well as a fatty acid and a nitrogenous base, but no phosphoric acid or glycerol

(1) *Galactolipids* —In addition to galactose and sphingosine, these compounds contain a single C_{24} acid molecule, either saturated (lignoceric acid [cerasine] and α-hydroxy lignoceric or cerebronic acid [cerebron]) or unsaturated (nervonic acid [nervone] and hydroxy nervonic acid [oxy nervone]) Cerebrosides occur largely in brain

(2) *Glucolipids* —These are similar to galactolipids, but contain glucose in place of galactose This compound was first isolated from the spleen in Gaucher's disease[11], it is also believed to occur normally in small amounts in this and in other tissues

3 Sulfolipids —These compounds contain a sulfate group

4 Gangliosides —These compounds are closely related to the cerebrosides They occur in the ganglion cells of nervous tissue, and in the spleen and erythrocytes They contain sphingosine, long chain fatty acids, hexoses (principally galactose although some glucose has been found), and a polyhydroxy amino acid called neuraminic acid,[11b]

5 Lipoproteins —These compounds found in mammalian plasma are composed of lipid material bound to proteins which electrophoretically migrate with α_1 and β_1 globulin fractions [11c] They are therefore designated α_1 and β_1 lipoproteins The lipid moiety of lipoproteins consists of mainly cholesterol esters and phospholipids containing principally stearic, palmitic and oleic acids although palmitoleic, linoleic and arachidonic acids have also been found [11d]

III DERIVED LIPIDS

Substances derived from I or II which still possess lipid properties such as solubility in ether and insolubility in water make up this class, which contains the most important components of the non saponifiable extract or non saponifiable fraction

1 Fatty Acids —This category includes all fatty acids obtained from natural products with carbon chains as long as that of caprylic acid (C_8), or longer Soaps are not included in this group

2 Alcohols —These are alcohols of higher molecular weight which are obtained on hydrolysis of waxes Glycerol which is water-soluble, is not a member of this group

(1) *Straight-chain Alcohols*.—Cetyl (C_{16}), and steryl (C_{18}) alcohols are the most common. ceryl (C_{26}) and myricyl (C_{30}) are less common members of the group.

(2) *Sterols*.—These contain the cyclopentanophenanthrene nucleus. Best known representatives are cholesterol, the phytosterols, sitosterol and stigmasterol and ergosterol.

(3) *Alcohols Containing the β Ionone Ring*.—This group is made up of vitamin A and carotenols. cryptoxanthin, zeaxanthin, and lutein.

3. HYDROCARBONS.—Compounds in this group include substances having no alcohol group which are fat soluble.

(1) *Aliphatic Hydrocarbons*.—These are present in liver fats, as well as in animal and plant waxes.

(2) *Carotenoids*.—These compounds possess no alcohol group and, in the main, have the empirical formula $C_{40}H_{56}$. β Carotene is the most important in this group. α- and γ-carotene and lycopene are other representatives.

(3) *Squalene*.—Squalene is related to carotenoids and is an intermediate in the biosynthesis of cholesterol. It is present in shark-liver oil.

4. VITAMINS D.—These vitamins are present in non-saponifiable extract but differ from steroids inasmuch as the steroid nucleus is ruptured.

5. VITAMINS E (TOCOPHEROLS).—These vitamins occur chiefly in vegetable oils as α-, β-, γ- or δ-tocopherols.

6. VITAMINS K.—This group includes derivatives of 1,4-naphthoquinone which possess long hydrocarbon side-chains. Their occurrence is extremely limited in fats and oils.

Properties of Fats and Oils

Physical Properties.—The most important physical property of fats is their melting point; this constant immediately determines under what conditions they will be present in the solid state and when in the liquid state. Those compounds which have a predominance of oleic, linoleic, and other unsaturated acids are usually liquid at the usual temperatures; on the other hand, fats which contain a preponderance of saturated acids such as stearic and palmitic are ordinarily solid. The melting point has an important nutritional bearing, since fats melting much above 50° C. (122° F.) are poorly utilized.

Although the proportion of long-chain unsaturated to saturated acids is of prime importance in establishing the physical state of the fat, it is not the only consideration. Arrangement of the fatty acids in the fat molecule is also of importance. Thus fats composed of the same fatty acids in the same proportion can be changed from liquid oils to partially solid fats by the process of *undirected interesterification* or to a mixture entirely solid at ordinary temperatures by so-called directed esterification.[4] These processes of ester interchange have been used in the preparation of newer types of lards now on the market. Although high temperatures will produce interesterification, the employment of catalysts (such as sodium methoxide) at ordinary temperatures will bring about the same result.

Fats and oils have a much lower specific gravity than do other components of the tissue. They are hydrophobic, and repel water and aqueous solutions. Fats have a lower surface tension than water; an interfacial tension is set up at the fat: water junction which varies in intensity with the fat and the aqueous solution which are in contact. The lower the interfacial tension, the more readily fat emulsions in water can be formed. When the interfacial tension is 0, complete homogeneity of the two media is to be expected. Interfacial tension is reduced by the phospholipids (particularly lecithin), by bile salts, and by such nonphysiologic agents as the Tweens. Because of this property, fats and related lipids have an important function in the cell membrane in controlling the permeability of the cell.

Another physical property of fat of especial importance is its caloric value. When fats are completely oxidized in the body, they yield 9.3 kilo-calories per gram, in contrast with this, proteins and carbohydrates give rise to only approximately 4.1 calories per gram. Actually, since fats are hydrophobic while carbohydrates and proteins are hydrophilic and hence are usually associated with water, the caloric value of fatty foods in comparison with foods containing carbohydrates and proteins is usually greater than 2.3, which is the ratio of caloric value of the pure foodstuffs. Obviously, fats are to be considered the foods possessing the highest caloric density of any of the foodstuffs.

Chemical Properties.—(*a*) *Unsaturated Linkages.*—The most important chemical properties of fat are those referable to the double bonds in the fatty acid chains. Fats will combine with iodine and with other halogens in proportion to the number of such double bonds. The so-called "iodine number" is a constant which gives information as to the degree of unsaturation of fats. Thus, coconut oil, composed largely of saturated fatty acids, has an iodine number of only 8 to 10. Butter fat has an I.V. (Iodine Value) of 26 to 38, while linseed oil has the exceedingly high I.V. of 177 to 209. Iodine values for common vegetable fats are as follows:[4] corn oil, 115 to 124, cottonseed oil, 105 to 115, olive oil, 79 to 90, peanut oil, 85 to 100, and soybean oil, 130 to 138. In contrast with these values, typical animal fats have the following iodine numbers: lard, 50 to 65, beef tallow, 35 to 45, and mutton tallow, 32 to 45.

The unsaturated bonds can be combined with hydrogen when the fats are subjected to a fairly high temperature in the presence of hydrogen gas together with finely-divided nickel, which acts as a catalyst in bringing about the combination of hydrogen with the unsaturated linkages. By means of this process, called *hydrogenation*, oils liquid at ordinary temperatures can be converted to fats, which are ordinarily solid. The extent to which the melting point may be increased depends upon the completeness of hydrogenation. On complete hydrogenation, most of the common animal and vegetable fats reach a maximum melting point of 65° C. (149° F.), which approximates the melting point of tristearin.

Hydrogenation is widely employed for converting the liquid oils into solid fats in the manufacture of shortenings and margarines. Two processes are available for the preparation of these hydrogenated fats, *i.e.*, either the partial hydrogenation of the total fat to the desired melting point

(35° to 48° C) resulting in the formation of isomers of the naturally occurring fatty acids or the complete hydrogenation of a portion of the fat, which is then mixed with sufficient of the unhydrogenated oil to give a blended fat with an appropriate melting point

The double bonds of fats are especially vulnerable to oxidation The addition of oxygen may take place at such linkages with the formation of oxides and peroxides, which eventually give rise to shorter chain acids and aldehydes These peroxides are powerful oxidizing agents, and they may destroy important vitamins present in the fats This is probably one of the reasons for the harmful nutritional effect of rancid fats However the spontaneous autooxidation of unsaturated fats is markedly inhibited by the presence of natural antioxidants in the fat The most important of these, which are widely distributed in vegetable oils, are the tocopherols (vitamins E) δ-Tocopherol is the most powerful antioxidant, while γ-β, and α-tocopherol have a decreasing potency as antioxidants The vitamin E effect is exactly opposite, α-tocopherol being the most powerful and δ tocopherol the least active form of the vitamin

In addition to the tocopherols, as antioxidants a number of other compounds have been found to retard rancidity, these are now widely employed in prolonging the shelf life of foods The commonest of these are NDGA (nordihydroguairetic acid), gum guaiac propyl gallate and gallic acid tannins, butylhydroxyanisole ascorbic acid (particularly its fatty acid esters) and others The antioxidant effect of the natural antioxidants such as tocopherols is markedly augmented if it is reinforced by the presence of synergists such as ascorbic acid

(*b*) *Saponification of Fats* —A second location at which all fats and oils are vulnerable is at the ester linkages where the fatty acids are combined with the alcohol groups of glycerol The fat molecules may be readily ruptured at these ester linkages, by heating with sodium or with potassium hydroxide Under such conditions, glycerol is set free, and the fatty acids are transformed to water-soluble soaps Although this type of saponification requires heat and strong alkali, it can likewise be effected at body temperature under physiologic conditions, by enzymes present in the secretions of the gastrointestinal tract It is a debated question to what extent saponification takes place in the digestion and absorption of fats The hydrolysis of fats is an important phenomenon not only in the digestion and absorption of fats and oils but also in their preservation One of the common reactions which causes the spoilage of fats occurs in so-called hydrolytic rancidity This is particularly well recognized in the case of rancid butter, in which the presence of free butyric acid produced in this manner is responsible for the development of the unpleasant odor and flavor associated with stale butter

DIGESTION AND ABSORPTION OF FATS IN THE GASTROINTESTINAL TRACT

Digestion in the Stomach

In the case of fats, no digestive changes take place in the mouth A certain mechanical separation of the fatty material from other foodstuffs

occurs in the stomach This separation is necessary as a prerequisite of digestion and absorption Thus, through the action of the *proteolytic* enzyme, pepsin, on proteins, and through the continuing catalysis of the breakdown of starch by the action of the salivary amylase, ptyalin in the stomach, most of the fat is set free from its admixtures with other foodstuffs

Although there is considerable evidence that a limited amount of lipolysis occurs in the fats while they remain in the stomach there is some question as to whether or not the lipase *responsible for* this splitting actually occurs in the gastric juice It may represent pancreatic lipase which has, to a certain extent, been *regurgitated into* this organ from the small intestine

The food remains in the stomach for variable periods before it is discharged into the small intestine, the length of time depending upon the quantity of fat present When the ingested food contains a large proportion of fatty material, digestion in the stomach is delayed After the food has been sufficiently digested and the fatty material has become emulsified, the chyme is discharged through the pylorus As much as three to four hours or even longer may elapse before all the chyme has been transferred from the stomach to the small intestine

Digestion and Absorption in the Small Intestine

The Action of Lipases —Steapsin, or pancreatic lipase, is the most important enzyme concerned with the digestion of fat in the entire gastrointestinal tract It is secreted in the pancreatic juice and can actively attack fat under conditions which exist in the small intestine Although it had been generally accepted that the fats were completely hydrolyzed to glycerol and fatty acids in the small intestine before absorption can occur, Frazer and Sammons[1] pointed out that on the basis of the time relations only a partial hydrolysis could be accounted for According to studies of Mattson and co-workers,[13] the action of pancreatic lipase is not a random one, but takes the form of a definite sequence of reactions on the triglyceride molecule forming diglycerides, monoglycerides and, finally, glycerol and fatty acids

In addition to pancreatic lipase, a small amount of lipase is present in the intestinal juice The presence of an enzyme lipoprotein lipase has been reported in some animal tissues This enzyme acts on triglycerides when they are combined with proteins, liberating free fatty acids [13a]

The Rôle of Bile in Fat Absorption —Although bile contains no enzymes which act on fat, it is essential for the absorption of fat, as well as for that of a number of other lipids, from the gastrointestinal tract It has generally been assumed that this effect *is related to the solvent action* exerted by the bile salts, which have the ability to reduce surface tension, with a resultant decrease in the interfacial tension at the water fat interface This promotes emulsification, and may actually result in a partial solution of the fats or fatty acids Borgstrom[13b] has reported that bile salts secreted into the small intestine decrease the pH optimum of pancreatic lipase to a value nearer that of the pH of the intestinal tract The bile salts are water-soluble compounds composed of the amino acid, glycine, or of the cysteine

derivative, taurine, conjugated with any one of a number of cholanic acids. The latter compounds have the steroid nucleus and appear to be derived from cholesterol or related compounds.

The Mechanism of Absorption of Fat.—There is adequate proof that ingested fat is absorbed from the small intestine after hydrolysis, as a result of the action of lipase, principally of pancreatic lipase. Bile acids are known to participate in some way in effecting absorption. After the fatty acids or fat gain entrance into the intestinal mucosa, the bile salt-fatty acid (or fat) complex is broken up; the bile salt is returned to the intestine to function in further fatty acid (or fat) transfer, and the free fatty acids, monoglycerides and diglycerides are changed to triglycerides. The neutral fat so formed is extruded in fine droplets from the basement membrane of the intestinal mucosa and gains entrance into the villi, from which it is carried *via* the lacteals and the lymphatic system to the blood stream.

The Rate of Absorption of Fats.—One of the most important indices of the nutritional value of fat is the rate of absorption. Although, under certain conditions, no differences may be observed between the total quantities of fats which can be utilized, as determined by digestibility studies, the *rate* at which they are utilized may be quite different. Fats having a low rate of absorption appear to be as well utilized as are fats which are rapidly absorbed when they are fed in low quantities. However, when fed in large doses, the slowly absorbed fat may not be removed from the intestine quickly enough to prevent a considerable loss in the feces. Moreover, the *maximum* amount of a fat which may be taken without causing digestive upsets, such as diarrhea, is directly related to the speed at which it can be utilized. It is thus evident that absorption rates and coefficients of digestibility, although related, afford information on independent physiologic responses to fat.

It is a moot question whether the rapid absorption of fat or the slow utilization of this foodstuff is to be preferred from the nutritional viewpoint. The fat which is more quickly absorbed has the advantage of being more rapidly available in the tissues; it is also less liable to produce digestive upset. On the other hand, fats which are more slowly utilized remain in the gastrointestinal tract over a more prolonged period, thus extending the period of satiety after a meal. In the second place, these fats tax the fat transport system less than is the case with the rapidly absorbed fats. It is possible that less extensive variations in blood fat levels are to be preferred to the more sudden changes in lipemia occurring when rapidly-absorbed fats are ingested. However, there are no data to indicate which type of physiologic response is preferable.

(a) *Absorption of Common Fats.*—Data on the rate of absorption of fats are quite limited. In the tests of Steenbock, Irwin and Weber[14] with butterfat, butter oil, cod liver oil, corn oil, halibut liver oil, lard and two shortenings, the following average percentages of fat were absorbed by rats at the several periods investigated: two hours, 24.1 to 40.8; four hours, 52.8 to 71.0; six hours, 67.5 to 86.4; eight hours, 83.4 to 95.6; and twelve hours, 97.4 to 99.6.

The rates of absorption of animal and vegetable fats by rats, based upon

mg/100 sq cm/hr over periods of three or four hours, are included in Table 16

(*b*) *Factors Affecting the Rate Absorption of Fats* —The common animal and vegetable fats are absorbed for the most part at rates between 60 and 40 mg per 100 sq cm of body surface per hour Of the common fats, oleo stock and palm oil, which have a larger proportion of stearic acid than do the more liquid fats and oils, are absorbed at a slower rate (30 mg per 100 sq cm per hour) Hydrogenated fats (*shortenings and margarine fat*) are absorbed at a rate comparable to that of the natural fats

TABLE 16 —THE COMPARATIVE RATES OF ABSORPTION OF ANIMAL AND VEGETABLE FATS (INCLUDING HYDROGENATED FATS) BY RATS, BASED UPON SURFACE AREA, OVER THE FIRST THREE OR FOUR HOUR PERIOD

Fat or oil	*Reference*	*Absorption rate mg/100 sq cm/hr*
Animal fats		
Butter oil	*a*	62 3
Halibut liver oil	*a*	60 8
Cod liver oil	*a*	58 8
Whale oil	*a*	54 0
Butterfat	*a*	53 0
Butterfat	*b*	51 1
Lard	*a*	50 0
Lard (rancid)	*a*	47 2
Lard prime steam	*c*	35 0
Oleo stock	*a*	31 4
Vegetable fats		
Linseed oil (raw)	*a*	58 5
Olive oil	*a*	54 4
Soybean oil	*a*	50 7
Corn oil	*a*	50 5
Peanut oil	*a*	50 0
Cottonseed oil	*a*	46 4
Cottonseed oil	*b, d*	39 2
Cocoa butter	*a*	43 1
Coconut oil	*b*	42 0
Coconut oil	*a*	41 2
Rapeseed oil	*b*	37 8
Palm oil	*a*	31 2
Hydrogenated fats		
Shortening A	*a*	46 5
Shortening B	*a*	45 7
Margarine fat (m p , 34° C)	*b, e f*	41 4
Crisco	*c*	37 1
Hydrogenated cottonseed oil		
(m p 46° C)	*d*	26 5
(m p 54° C)	*d*	18 0
Hydrogenated lard		
(m p 48° C)	*c*	34 5
(m p 55° C)	*c*	20 7

a = From data of Steenbock, Irwin and Weber J Nutrition, *12* 103, 1936
b = Deuel, Hallman, and Leonard J Nutrition, *20*, 215 1940
c = Crockett, and Deuel J Nutrition, *33*, 187, 1947
d = Augur Rollman and Deuel J Nutrition *33*, 177, 1947
e = Calbert, Greenberg, Kryder and Deuel Food Research, *16*, 294 1951
f = Bavetta, Hallman, Deuel and Greeley Am J Physiol, *134*, 619, 1941

The most important factor which influences the rate of absorption of fats is their melting point. The somewhat slower rate of absorption of oleo stock and palm oil can be attributed in part to this phenomenon; moreover, the lowest rates of absorption exhibited by any fats were those of hydrogenated lard and hydrogenated cottonseed oil melting at 54° to 55° C.

Another factor which influences the rate of fat absorption is the size of the dose. The speed at which fats leave the intestine is increased somewhat when higher doses are given. It is believed that this may account for the fact that fats are absorbed most rapidly during the early hours after the administration of large dosages.

Although no sex differences in the speed of fat absorption can be demonstrated in the case of man, there are differences in the rate of utilization which are referable to age. Thus Sobel *et al.*[15] and Tidwell, Holt, and co-workers,[16] demonstrated that babies under one year of age absorb fats quite inefficiently. On the other hand, Becker and associates[17] have shown that fat is absorbed and metabolized more slowly in the aged than in the case of younger subjects.

The presence of emulsifying agents not only increases the rate of absorption of fats, but also, in the case of poorly utilized fats, augments the extent of their digestibility. Although Augur and co-workers[18] noted that it was impossible to increase the complete digestibility of cottonseed oil by the addition of lecithin, they did report that the *rate* of absorption was increased by about 50 per cent when the phospholipid was added. Moreover, the susceptibility of rats to diarrhea, caused by the administration of a large dose of cottonseed oil, was decreased from 40 to 10 per cent by the simple expedient of adding 20 per cent of lecithin to the cottonseed oil. In the case of poorly utilized samples of hydrogenated cottonseed oil melting at 46° C. and 54° C., the rate of absorption was augmented from 50 to over 100 per cent by the addition of lecithin; the total digestibility was also correspondingly improved.

In addition to lecithin, another emulsifying agent, namely, Tween 80 (polyoxyethylene sorbitan monooleate), has been reported by Jones *et al.*[19] to decrease markedly the loss of fat in the feces in sprue. Tween 80 also greatly improved the fat utilization in certain disorders of the pancreas resulting from infections in various portions of the gastrointestinal tract, and following subtotal gastrectomy.[19,20]

The speed of absorption of simple fats composed of short-chain acids has been found to decrease with the lengthening of the fatty acid chain. Triacetin is the most rapidly absorbed.[1] Another interesting variation occurs in the case of triglycerides composed of fatty acids with an odd number of carbons; the latter fats are more slowly utilized than are the corresponding even-chain triglycerides. Similar variations in the absorption rate of the short-chain acids composed of odd- and even-chain acids were also noted.[2]

There is some question as to whether or not the absorption of fats is related to the secretion of the adrenal cortex. The importance of the adrenal cortex in fat absorption was first demonstrated by Verzár and Laszt;[3] these results were confirmed by Bavetta *et al.*[4] However, the adrenal cortex does not control the absorption of triglycerides composed of fats in which the fatty acids are water soluble.[5,6]

Digestion and Absorption in the Large Intestine

The digestion and absorption of fats is practically complete before the intestinal contents reach the large intestine It is now known that instead of absorption of fatty materials occurring in the large intestine, lipids are actually excreted through the walls of the large intestines These consist of fatty acids similar to those in the plasma, of cholesterol, and of the higher aliphatic alcohols, cetyl and stearyl[27, 8] That "secretion" must take place is indicated by the fact that the total content of these lipids *in the intestinal mucosa is sufficient to account for only* a small fraction of the amount eliminated[9] The lipids secreted into the large intestine become part of the fecal lipids

DIGESTIBILITY OF FATS AND OILS

The coefficient of digestibility of fats constitutes one of the most important indices of the nutritional value of this foodstuff This term represents the percentage of the ingested foodstuff which gains entrance into the body and hence is not lost in the feces In the case of fats, the coefficient of digestibility is expressed by the following ratio

$$\frac{\text{Fat ingested} - \text{fat excreted (corrected for metabolic fat)}}{\text{Fat ingested}} \times 100$$

The Comparative Digestibility of Various Fats and Oils in Man

In general, animal and vegetable fats are practically completely utilized, *i e*, they have a coefficient of digestibility above 94 Table 17 illustrates results which have been recorded by a number of investigators on common fats and oils

Oleomargarines are as well digested as are other fats and oils Holmes[30] reported coefficients of digestibility, in human subjects, of 97 2, 93 4, and 96 8 for three types of oleomargarine made before 1925, while Deuel[31] recorded a figure of 96 7 for a modern type of margarine made from hydrogenated vegetable oil

Fats melting at temperatures above 50° C (122° F) are less efficiently utilized than are fats having lower melting points or those which are liquid at ordinary temperatures The values obtained with deer fat, mutton tallow, and oleostearin, as recorded in Table 15, are distinctly lower than *the figures for the other fats Moreover, some* values lower than 90 have been reported for vegetable fats hydrogenated to a melting point of 50° C or above The following are the lowest values noted straight hydrogenated peanut oil (m p, 52 4° C), 79 0,[3] straight hydrogenated corn oil (m p, 50° C), 88 5[32] and blended hydrogenated cottonseed oil (m p, 50° C), 87 0[33]

Factors Affecting the Digestibility of Fats and Oils

In general, the same factors which influence the rate of absorption may also affect the extent of utilization of fats Thus, as already noted, fats

having melting points above 50° C may have a coefficient of digestibility markedly lower than the usual figure of 95 or more. Some workers consider that the proportion of stearic acid in the compound (which usually increases with a rise in melting point) is the deciding factor in reducing digestibility. This is not necessarily the case, as is shown by the fact that marked variations in digestibility obtained when mixed triglycerides were fed, as contrasted with the results when mixtures of simple triglycerides of similar composition were given.[34]

TABLE 17.—AVERAGE COEFFICIENTS OF DIGESTIBILITY OF COMMON VEGETABLE AND ANIMAL FATS AND OILS IN NORMAL HUMAN SUBJECTS*

Fat or oil	*Coefficient of digestibility*	*Fat or oil*	*Coefficient of digestibility*
Vegetable fats and oils		*Vegetable fats and oils*	
Almond	97.1	Soybean	97.5
Apricot kernel	98.4	Sunflower seed	96.5
Avocado	87.8	Teaseed	91.2
Black walnut	97.5	Tomato seed	95.8
Brazil nut	96.3	Watermelon seed	94.8
Butternut	95.4		
Charlock	98.9	*Animal fats and oils*	
Cherry kernel	98.0	Bacon	96.7
Cocoa butter	94.9	Beef (m.p. 45° C.)	93
Coconut	97.9	Brisket	97.4
Cohune palm	99.1	Butter	97
Corn	96.9	Chicken	96.7
Cottonseed	97.2	Cod liver	97.7
Cupuassu	94.1	Cream	96.9
English walnut	97.6	Deer (m.p. 51.4° C.)	81.7
Hempseed	98.5	Egg yolk	93.8
Hickory nut	99.3	Fish	95.2
Japanese mustardseed	98.8	Goat's butter	98.4
Java almond	97.0	Goose	95.2
Melon seed	98.2	Hard palate (m.p. 34° C.)	93.7
Olive	97.8	Horse	93.9
Palm kernel	98.0	Kid	95.3
Peach kernel	96.6	Lard	97
Peanut	98.3	Mutton (m.p. 50° C.)	88
Pecan	96.8	Oleo	96.8
Poppyseed	96.3	Oleostearin (m.p. 50° C.)	80.1
Pumpkin seed	98.2	Ox marrow	93.5
Rapeseed	99.0	Ox tail	96.6
Sesame	98.0	Turtle	98.6

* Adapted from Deuel, *The Lipids*, Vol. *II*, Biochemistry, Digestion, Absorption, Transport and Storage, Interscience, New York, 1955.

Polymerization of fats, produced by heating them at high temperatures (250° to 275° C.), may result in a marked reduction of the coefficient of digestibility. When fats are subjected to such heat treatment, not only are physical properties altered (as demonstrated by increased viscosity) but also chemical changes may obtain (as shown by the decrease in iodine number). Crampton *et al.*[35] reported that the efficiency of diets containing

polymerized fats in maintaining the growth of rats was decreased below that of similar diets containing unheated fats. Lassen, Bacon, and Dunn[36] noted that the digestibility of fats was progressively decreased concomitantly with their increased exposure to heat. However, the effect of subjecting fats to the temperatures ordinarily employed for frying (205° to 210° C) has been shown to be without deleterious effect on digestibility.[37]

Although emulsifying agents such as lecithin do not increase the coefficient of digestibility of oils, such as cottonseed oil, which are ordinarily completely utilized, they do increase the rate of absorption, as well as the capacity to utilize large doses without the production of diarrhea. However, Tween 20 (polyoxyethylene sorbitan monolaurate) has been shown to increase fat retention to only a slight extent in the case of premature infants.[38]

Another factor largely unrecognized which may alter the extent of utilization of fats is the foodstuff fed along with them. Barnes, Primrose, and Burr[39] first pointed out that fats are digested to a lesser extent on a low-protein diet than on a high-protein regimen. The variations are, however, minor. Several other investigators have confirmed these findings. The most important dietary component which influences fat utilization is calcium. When high calcium diets were fed to rats, the proportion of fats digested was decreased. Cheng *et al.*[40] found that the intensity of the effect varied with the proportion of calcium added to the diet, as well as with the composition of the fat employed. The most marked effects were noted with fats having lauric, myristic, palmitic and stearic acids as their fatty acid components, while the digestibility of natural fats containing a high proportion of oleic and linoleic acids was not appreciably influenced by the presence of calcium.

In addition to the effect of the nature of the fat, the extent of digestibility depends to some extent upon the individual ingesting the fat. There is some evidence that, at least in the case of rats, a slightly higher digestibility may obtain in females as compared with males.[41] Although mature female rats digested more fat than did male rats when fed *ad libitum*, no sex difference was apparent in young growing rats or in pair-fed adults.[41a] Just as the absorption rate of fats was found to be lower in the case of infants and young children than in the case of older children and adults, so the digestibility has also been found to be depressed.[42] Reduced coefficients of digestibility were particularly the rule with premature infants.[16]

Different species of animals exhibit differences in the digestibility of fats. Although fats are apparently well utilized by most species of animals, guinea pigs have a less efficient utilization, particularly of the higher-melting fats.[41] Extensive digestibility studies on human subjects were reviewed by Langworthy,[43] and the entire subject has been treated by Deuel.[41]

THE ABSORPTION OF LIPIDS OTHER THAN FATS AND OILS FROM THE GASTROINTESTINAL TRACT

The absorption of non glyceride components present in fat is so closely tied in with the utilization of fat itself that it is of importance to consider this topic briefly at this point. The association between the absorption of

phospholipids and cholesterol on the one hand and that of the triglyceride fats on the other hand, is particularly close

The Absorption of Phospholipids

From the quantitative standpoint, lecithin is the phospholipid which is of greatest importance both in the foods and in the tissues It was formerly believed that a more or less complete hydrolysis of lecithin to its several components was a prerequisite of absorption Thus lecithinase B an enzyme present in pancreas, which is probably distinct from steapsin or other pancreatic lipase[44] is able to hydrolyze the 2 fatty acids from lecithin leaving glycerylphosphorylcholine The latter compound can be completely hydrolyzed to glycerol phosphoric acid and choline by alkaline phosphatase However Artom and Swanson[45] employing P^{32} incorporated into lecithin or fed as orthophosphate together with unlabeled lecithin reported a considerable increase in the amount of labeled phospholipid in the former case This was interpreted to mean that part of the phospholipid must be absorbed without hydrolysis Bile is considered to be essential for the absorption of lecithin[46]

The Absorption of Aliphatic Alcohols and Waxes

Waxes which are lipids composed of higher monatomic alcohols (rather than glycerol) and fatty acids are less readily absorbed than are most glyceride fats In some cases, this results from their relatively high melting point Another factor which may contribute to the poor utilization of waxes is the sluggishness with which the ester linkage is split, although there is no definite evidence that such a cleavage is a prerequisite for absorption

The Absorption of Cholesterol and of Other Sterols

Cholesterol is readily absorbed from the small intestine whether it is given in the form of the free alcohol or as the ester[47,48] In either case the cholesterol present in the chyle consists of fairly constant porportions of this sterol as the free alcohol (30 per cent) and in ester form 70 per cent)

In the case of several species of animals (rats chickens and guinea pigs) the absorption of cholesterol from the gut does not take place to any considerable extent in the absence of fat however in the case of the rabbit the absorption of cholesterol from the gastrointestinal tract proceeds quite efficiently when the diet contains no fat Bile salts are an even more important factor in stimulating the absorption of cholesterol than is the solvent action of fat Siperstein and co-workers[49] employing C^{14} labeled cholesterol, concluded that bile plays an obligatory role in the passage of cholesterol from the gastrointestinal lumen to the lymph

Cholesterol is the only commonly-occurring sterol which is capable of considerable absorption from the gastrointestinal tract Only ostreasterol which is a C_{29}-sterol obtained from oysters and other molluscs resembles cholesterol in being capable of absorption[50] Certain plant sterols which

are poorly absorbed have been reported to decrease the absorption of cholesterol in several species of animals.[50a] This may be due to competition for an enzyme, presumably cholesterol esterase, which is widely distributed in the intestine.[50b]

In the case of man, Burger and Winterseel[51] reported an absorption of cholesterol as high as 50 per cent when 5 gm. of the sterol were fed with 100 gm. of olive oil. Other investigators reported comparable results. In his review of the absorption and excretion of lipid and cholesterol in man and other animals, Cook[5] states that the absorption in man is not marked, but that it continues at a fairly constant level.

The Absorption of Carotenoids and of Fat-soluble Vitamins

The same conditions which are required for the absorption of glyceride fats are essential for the utilization of the carotenoids and of most of the fat-soluble vitamins. The presence of the bile acids is the most important of these factors.

The Importance of Bile in Absorption.—Greaves and Schmidt[53] were the first to establish the necessity of bile in the absorption of β-carotene. In contradistinction to carotene, vitamin A does not require bile for its absorption.[54] The most conclusive proof that bile is necessary for the utilization of vitamin D was the demonstration by Greaves and Schmidt[5] that little or no irradiated ergosterol was absorbed from the gastrointestinal tract of bile fistula rats, while appreciable amounts of this vitamin were carried across the intestinal wall of the bile fistula rat when desoxycholic acid was given orally. Greaves and Schmidt[56] demonstrated that the tocopherols (vitamins E) are not absorbed when fed to choledochocolostomized rats. Hogs having bile fistulas have also been shown to be incapable of absorbing these vitamins.[57]

The discovery of vitamin K was due to the production of deficiency symptoms when a bile deficiency occurred. After ligation of the bile ducts, a reduction of prothrombin and a consequent decrease in blood coagulability was noted with chickens, rats and dogs. Greaves and Schmidt[58] reported that the symptoms of deficiency of vitamin K in rats could be corrected by the oral administration of the vitamin. Desoxycholic acid is believed to be the bile component responsible for aiding in the absorption of vitamin K from the gastrointestinal tract.[59] In the case of man, it has long been known that a hemorrhagic tendency is present in cases of obstructive jaundice; this condition can be successfully treated by the administration of vitamin K with bile or bile salts.[60,61]

The Effect of Fat Feeding.—The absorption of β-carotene occurs most satisfactorily if it is given in a fat medium. This is true not only for rats, chickens, and cats, but also for man. The presence of fats is much less important in the absorption of vitamin A or of any of the other fat-soluble vitamins than it is for the utilization of carotene.

The Effect of Emulsifying Agents.—Lecithin has been shown to enhance the utilization of carotene in man,[6] as well as in the rat. In fact, margarine has been shown to be an especially effective vehicle for administering carotene, presumably because of the emulsifying agents which it contains.

Lecithin has likewise been found to improve the utilization of vitamin A. When aqueous dispersions of carotene and of vitamin A are employed, they are apparently much better utilized than is the case with oil solutions of these vitamins. Although emulsifying agents are presumably equally effective in improving the utilization of the other fat-soluble vitamins, the demonstration of this fact has been less satisfactory than in the case of carotene and vitamin A.

The Effect of Mineral Oil.—The effectiveness of carotene as a source of vitamin A is much reduced when mineral oil is given simultaneously with the provitamin A. Dutcher *et al.*[63] showed that the deleterious effect of mineral oil on the utilization of carotene is much more pronounced than it is on that of vitamin A. Mineral oil has likewise been reported to impair the absorption of vitamin D,[64] and especially of vitamin K; in the latter case the effect has been demonstrated not only in rats[65, 66] but also in man.[67]

The Absorption of Hydrocarbons

The earlier work was interpreted to mean that aliphatic hydrocarbons are incapable of absorption from the gastrointestinal tract, since a practically quantitative recovery of administered hydrocarbons could be obtained in the feces and none could be demonstrated in the chyle. However, more recent experiments, particularly those of Channon and co-workers,[68, 69] El Mahdi and Channon,[70] and especially the work of Stetten[71] with isotopically tagged *n*-hexadecane, have forced one to modify the earlier concept. Daniel, Frazer, French, and Sammons[7] were able to demonstrate that, when paraffin was given to rats in a 50 per cent solution in olive oil in a fine emulsion, over 60 per cent of the mineral oil was absorbed over a three hour period. Hydrocarbons are likewise known to form coordination compounds with desoxycholic acid. Another fact which indicates that aliphatic hydrocarbons have a physiologic significance is their widespread distribution in plant products.[41]

THE TRANSPORT OF FATS AND OF OTHER LIPIDS TO THE TISSUES

Changes Taking Place in the Intestinal Mucosa

According to both the Lipolytic Theory and the Partition Theory, triglyceride fats are resynthesized in the intestinal mucosa; in the former case by the combination of fatty acids and glycerol, and in the latter by the combination of fatty acids with partial glycerides. It has been postulated that this synthesis involves the formation of a phospholipid, presumably lecithin, as an intermediate. According to this scheme, lecithin breaks down to give a diglyceride and a base which must be phosphorylcholine. The diglyceride is changed to a triglyceride molecule which is transferred through the basement membrane of the intestinal cells to the lacteals in the villi. The choline base presumably regenerates new lecithin by combination with new glycerol and 2 fatty acid molecules. However, turnover studies

of Zilversmit *et al.*[3] and of Schmidt-Neilsen,[74] using P^{32}, indicate that phospholipids are not obligatory intermediates in the passage of fat through the intestinal wall. Artom and Cornatzer[75] demonstrated that fat absorption proceeds without phospholipid formation in the intestine of choline deficient rats. Reiser[75a] has also concluded that phospholipids are not intermediates in the formation of triglycerides but that probably the reverse condition exists.

The intestinal mucosa mediates changes in lipids other than fats, which are directly or indirectly concerned with the absorption of these latter compounds. Thus cholesterol may be esterified or hydrolyzed in the intestinal mucosa. The proportion of cholesterol esterified in the lymph is the same, irrespective of whether the cholesterol is given in the free or in the ester form. According to Swell and collaborators[76] the pancreatic secretion is the major source of cholesterol esterase in the rat intestinal mucosa.

Mattson[76a] has indicated that the intestinal wall may be capable of changing the degree of saturation and also the chain length of absorbed fatty acids.

It was first suggested by Sexton and associates[77] that the conversion of β-carotene to vitamin A in such animals as rats, in which carotene is not present in the blood or tissues, takes place in the intestinal wall. Later results of Mattson *et al.*[78] proved that the change β-carotene → vitamin A, actually takes place in the intestinal wall. These results have been confirmed by many investigators, in the case of the chicken, guinea pig, pig, goat, sheep, and rabbit. α-Carotene and cryptoxanthin, which are partially converted to vitamin A, also undergo this change in the intestinal mucosa. It is not known whether or not any transformation of carotene takes place in the intestine in the case of man.

The esterification of vitamin A is likewise a function of the intestinal wall. This is indicated by the fact that vitamin A appears in the chyle of the rat and pig largely in the form of the ester, irrespective of whether vitamin A alcohol, vitamin A ester, or β-carotene has been administered. The esterified vitamin A in the intestinal wall approximates 75 per cent of the total.[79]

Another reaction mediated by the intestine, which is not directly connected with absorption, is the transformation of retinene (vitamin A aldehyde) to vitamin A. It has been shown that retinene₁ is changed to vitamin A_1,[80] while retinene$_2$ is converted to vitamin A_2.[81]

The Transport Via the Lymphatics and Portal Vein

The Transport of Fat.—The information is fragmentary as to how fats and other lipids are transferred from the epithelial cells to the villi for transport to the liver and other tissues by way of the lacteals and lymphatics or through the capillaries and portal system. The fat droplets become larger toward the interior of the cell, and it is believed that such droplets are extruded from the basement membrane of the intestinal cells into the extracellular spaces of the villi. The older theory of Schafer,[8] which ascribes the transfer of the fat droplets to the lacteals as a function of the leucocytes, and that of Heidenhain,[83] which relates this phenomenon to

the pumping movements of the musculature of the villi have not been disproved or replaced by newer theories On the other hand, the hydrolysis-resynthesis theory of Loevenhart[84] which postulates hydrolysis and resynthesis of fat whenever it passes through a cell membrane is not now generally accepted

Two pathways are available for transport of the fat and other lipids from the villi to the liver and other tissues One of these routes involves the lacteals, the intestinal lymphatics, the thoracic duct, the subclavian vein and finally the systemic blood stream The second pathway involves the capillary network of the villi the larger intestinal blood vessels, and finally the portal circulation to the liver

It is now believed that practically all of the triglyceride fats and in act, other lipids, follow the lymphatic route in their transfer from the in stine to the organs of the body Bloom *et al*,[85] using isotopically-tagged ipalmitin were able to recover as much as 92 per cent of ingested fatty ids from the lymph of rats during the period up to nineteen or twenty-ir hours after the feeding The fat present in the lymph was in the form triglycerides, irrespective of whether fatty acids monoglycerides or triglycerides had been fed Moreover the composition of fats in the chyle varied from that of the ingested fats

In spite of the fact that the bulk of fat is transported in the lymph one must still accept the possibility that a small proportion travels by way of the portal circulation There is general agreement that the volatile fatty acids may be absorbed by the portal vein as first suggested by Raper[86] Bloom and associates[87] proved that in addition to acetic, butyric and caproic acids decanoic acid and to a lesser extent lauric acid are also transported by the portal route Although it is not clear whether such lower fatty acids appear in the portal blood as the free acids as their salts or as the triglycerides Frazer[88] accepted as part of his Partition Theory the assumption that the absorption of short-chain triglycerides occurs after hydrolysis *via* the portal circulation

Transport of Lipids Other Than Fats—The lymphatics are also the chief route of transport of the lipids other than triglycerides from the gastro intestinal tract to the liver and other tissues The lymph phospholipid may owe its origin partly to neutral fat and partly to phospholipid synthesized from various decomposition products of lecithin however Artom and Swanson[45] proved that some of the chyle lecithin definitely represents phospholipid which has been absorbed without hydrolysis from the gastrointestinal tract

According to Chaikoff and co-workers,[89] absorbed cholesterol can be quantitatively accounted for in the lymph it is therefore doubtful whether any appreciable proportion is transported from the intestine by way of the portal circulation Biggs, Friedman and Byers[90] also proved that the lymphatic system provides the pathway for conveying cholesterol from the intestine to the systemic circulation

Drummond Bell and Palmer[91] proved as early as 1935 in the case of a patient suffering from chylothorax that carotene and vitamin A are carried in the chyle Their failure to recover all of the administered carotene in the chyle may simply indicate that some of the pigment is split

into vitamin A in the intestinal wall in the human subject, and is carried as such in the chyle

Vitamin A is also transported in the lymph, as shown in the case of chylothorax in a human patient, cited by Drummond *et al* [91] It has since been reported that this vitamin follows the same route of absorption in the case of the rat, pig, and bullock as in man The fact that the portal vein plays no role in the transport of vitamin A from the intestine has been repeatedly confirmed by a number of different investigators A considerable proportion of the vitamin A in the lymph occurs in ester form, irrespective of whether it was administered in the form of the vitamin A ester, vitamin A alcohol or even as the provitamin, β-carotene [79 9]

Little information is available concerning the route of absorption of vitamins D, E, and K However, there is strong presumptive evidence that these fat-soluble vitamins behave in the same manner as β-carotene and vitamin A insofar is the pathway of absorption is concerned The fact that vitamin K deficiency can be produced rapidly when the intestinal lymph is drained externally offers an excellent proof that natural vitamin K is absorbed by the lymphatic pathway [93 94] However, it may be possible that a synthetic vitamin K, such as menadione, which is water-soluble rather than fat-soluble may follow the portal system

THE LIPID COMPOSITION OF THE BLOOD

All lipids which are present in the tissues occur to a greater or lesser extent in the blood Although the lymphatics provide the initial pathway for transporting most lipids from the intestinal tract, the blood is the ultimate avenue for the further distribution of these products to the liver and other tissues

The Normal Composition of the Blood Plasma

The levels of blood lipids under most conditions are extremely uniform in any one individual except as they are affected by the ingestion of fatty foods Moreover, the composition of the fasting bloods of different normal individuals shows quite constant values The figures as recorded by Boyd [95] for the plasma lipids of normal women under controlled conditions of diet, exercise, and rest, are as follows (expressed in mg per cent) total lipids 589 neutral fat, 154 total fatty acids, 353, consisting of phospholipid fatty acids 130, cholesterol ester fatty acids, 77, and neutral fat fatty acids, 146, total cholesterol, 162, consisting of combined cholesterol, 115, and free cholesterol 47, and phospholipids, 196 Wide variations are recorded for blood carotene (6 to 312 µg per cent), while vitamin A (35 to 40 I U per cent) and α-tocopherol (0 6 to 1 6 mg per cent) show a more restricted range [96] Unsaturated fatty acids have been reported to have the following average value and range in the plasma of normal adults,[97] expressed in mg per cent oleic, 700 (250 to 950), diene, 70 (15 to 115) triene, 12 (5 to 35), and tetraene, 45 (35 to 65)

Neutral fat occurs in blood plasma largely in the form of fine particles which are commonly referred to as "chylomicrons" They have a diameter of one micron or less It is believed that they are stabilized by protein

films which form on their surfaces It was formerly believed that the non-glyceride components of blood lipids (such as phospholipids, cholesterol, carotenoids, and fat-soluble vitamins) were carried in blood plasma in solution in the fat droplets However most investigators are now of the opinion that these latter components are transported in the blood in more or less firm combination with specific plasma proteins, which are referred to as lipoproteins

The Composition of Formed Elements

The erythrocytes vary markedly in composition from the blood plasma The red cells contain no neutral fat although fatty acids occur in combination with phospholipids and possibly with cholesterol Cerebrosides appear in these cells, but are not found in the plasma

Phospholipids are present in approximately double the concentration in cells as in the plasma The nature of the phospholipids in the cell differs from that in the plasma for example whereas cephalins make up only 10 per cent of the plasma phospholipids, they account for 50 to 60 per cent of that in the cells In the case of cholesterol, the quantity is somewhat lower in the cells than in the plasma Whereas cholesterol esters were found to comprise approximately 70 per cent of the total plasma cholesterol the concentration in red cells has been reported to be from 0 per cent to 20 per cent [97, 98, 99]

Leukocytes have a higher proportion of total lipids than either plasma or red blood cells Leukocytes likewise contain an appreciable amount of neutral fat Boyd[99] reported the average composition of leukocytes from the blood of women (in mg per cent) as follows total lipid 1710 ± 734 neutral fat 536 ± 536 total fatty acids 1103 ± 614 phospholipid fatty acids 534 ± 170 cholesterol ester fatty acids 75 ± 65 neutral fat fatty acids, 508 ± 508, total cholesterol 300 ± 60 free cholesterol 194 ± 110, combined cholesterol 110 ± 97 and phospholipids 802 ± 255

Lipoproteins in the Blood

β Lipoprotein contains about 75 per cent of the blood lipid of the normal fasting man although this protein constitutes only 5 per cent by weight of the total plasma proteins [100] These proteins are euglobulins of spherical shape having a molecular weight of approximately 1 300 000 The β lipoprotein fraction has been reported to have the following composition [101] protein 25 per cent phospholipids 30 per cent and cholesterol (esterified and free) 45 per cent Approximately 75 per cent of the hydrocarbon carotenoid in the plasma is found in the β lipoprotein fraction [102]

α Lipoproteins are a second lipid-containing protein in blood plasma Although they comprise only about 3 per cent of the total plasma proteins they may contain as much as 35 per cent of the total plasma lipids The α-lipoprotein molecule has an ellipsoid form with a molecular weight of approximately 200 000 [103]

Presumably a large number of different lipoproteins occur in the blood Different proteins probably combine with the several lipid components Ganguly and co-workers[104] and others[105] reported that vitamin A ester and

vitamin A alcohol are associated with different protein fractions in the plasma, while lutein and β-carotene appear to be combined with still another fraction It has been suggested that three types of lipoprotein linkage occur in horse serum, namely, loose association, cenapse, and a very strong bond in β_1-lipoprotein [105] A very comprehensive review of blood lipoproteins is found in Discussions of the Faraday Society [106]

Factors Altering the Lipid Composition of the Blood

The levels of the three main lipid components of the plasma, *i e*, neutral fat, phospholipids, and cholesterol, are interrelated Conditions affecting the level of any one of these components usually causes an alteration of the other two

The most important factor which increases the level of blood lipids is the ingestion of fats A hyperlipemia obtains after fat ingestion, which reaches its maximum in four to six hours, after which the lipid values return to the preprandial levels Not only is the level of neutral fat increased by the ingestion of fat, but also that of blood phospholipids Quite variable results have been reported on the effect of fat ingestion on the level of blood cholesterol Many investigators note that a rise in blood cholesterol occurs concomitantly with increased fat consumption

On further investigation it has been shown that there is a difference in the cholesterolemic effect of saturated animal fats and the more highly unsaturated vegetable oils, animal fats containing long chain saturated fatty acids tend to raise the serum cholesterol concentrations whereas vegetable oils containing high concentrations of polyunsaturated fatty acids in general tend to decrease serum cholesterol levels [106a] Although Anderson and Keys[107] found that serum cholesterol levels decreased appreciably in patients on a fat-free diet, Beveridge[107a] has obtained comparable decreases in serum cholesterol using low fat diets and diets rich in corn oil, and Kinsell[107b] has decreased serum cholesterol levels by the addition of essential fatty acids to the dietary regimen Alfin-Slater *et al* [108] noted a decrease in plasma cholesterol levels in rats on a completely fat-free diet, however, the cholesterol level in the liver and adrenal glands was simultaneously increased It is postulated by the latter workers that the essential fatty acids are required for the transport of cholesterol

The ingestion of phospholipid was shown to cause a marked and persistent hyperlipemia, and neutral fat was found to be the first component affected [109] On the other hand, there are divergent opinions as to whether or not the ingestion of cholesterol causes a hypercholesterolemia in man In the case of the lower animals, there is considerable experimental evidence that a hypercholesterolemia results when cholesterol is included in the diet, especially when bile salts are also present to facilitate absorption of the sterol The administration of cholesterol to rabbits has been shown to cause an increase in plasma phospholipids,[110] as well as in all blood-lipid constitutents [111]

Fasting is another condition which may cause an alteration in the blood lipids A generalized hyperlipemia usually occurs in man during fasting,[112 113] on the other hand, there is less evidence that fasting provokes a

hyperlipemia in other animals. Rats and dogs are particularly resistant to changes in blood lipids during inanition.

Age is another condition which may to some extent affect blood lipids. Cholesterol is the chief component concerned. The proportion of this sterol in the plasma of the newborn is especially low. However, the level of blood cholesterol reaches the adult level by the age of seven months. There is some difference of opinion as to any further effect of age on blood cholesterol. Page and collaborators[114] reported that this substance remained at an essentially constant level in a large group of men varying in age from twenty to one hundred and one years, and Sperry and Webb[115] found that an increase in blood cholesterol was not an obligatory concomitant of aging in patients studied over a period of fifteen years. However, Keys[116] maintains that the blood cholesterol of normal men increases with age. The average level reported by the latter investigator increased from an average of 173 mg. per cent at the age of nineteen years to 252 mg. per cent at fifty-two years. The average rise is believed to amount to 2.2 mg./100 ml. plasma/year. In studies performed on men in Italy and in Spain, Keys and coworkers[116a,b] found that in both groups the serum cholesterol rises until the third or fourth decade of life and then levels off.

Although no variations in the concentration or in the partition of the major blood lipids are ascribable to sex, the level of ketone bodies in the blood is closely linked to sex, being markedly higher in the ketosis of fasting in women than in men. No variations in the blood picture can be correlated with race. Alterations in the levels of blood lipids may obtain during the menstrual cycle, as well as during pregnancy. Lorenz and co-workers[117] reported phenomenal increases in blood fat, and especially in plasma phospholipids, in the fowl, with less spectacular increases in blood cholesterol, associated with the onset of egg production.

In the case of carotene, the blood levels have been found to be consistently higher in women than in men, on the other hand, the opposite phenomenon obtains insofar as blood vitamin A is concerned. Week and Sevigne[118] demonstrated, in a large number of tests, that plasma vitamin A values were consistently lower in their female subjects than in their male subjects, not only during fasting but at all periods up to twenty-four hours after the administration of 134,000 μg. of vitamin A.

For a discussion of changes in the blood lipid patterns as associated with disease, the reader is referred to Peters and Van Slyke[119] and to Deuel.[41]

THE STORAGE OF FAT IN THE ANIMAL BODY

Lipids are present in all cells of the body in which they exercise special functions, such as those concerned with structure, metabolism, and permeability of the cell. These functional lipid components of the cell represent a relatively stable fraction, and the proportion is influenced very little by variations in intake. They are composed principally of phospholipids, cholesterol, and cerebrosides. Terroine[120] assigned the name of *element constant* to this fraction of lipids.

On the other hand, the so-called *element variable* of Terroine represents the depot or storage fats; these occur in such locations as under the skin

(subcutaneous), in the peritoneal cavity (omental and mesenteric), around the kidney (perirenal), surrounding the ovary (ovarian and genital) as well as in the muscles (intramuscular). In contradistinction to the constant element, the quantity of depot fat stored is exceedingly variable, depending upon a number of physiologic conditions such as diet, age, sex, species and hormone balance. Although it was formerly believed that adipose tissue representing the fat deposits was an accumulation of inert material which possessed little or no metabolic activity, it is now accepted that the fatty tissues constitute an important link in the metabolic processes of the animal. Such adipose tissue possesses the ability to transform glycogen to fat. It exhibits a normal metabolism characteristic of living protoplasm rather than the absence of respiration which would be expected if it were completely inert tissue. An excellent review of adipose tissue was contributed by Wertheimer and Shapiro.[121]

Factors Altering Normal Fat Storage

Diet.—Although diet has a profound effect on the composition and quantity of the depot fat laid down, it exerts only a minor effect on the distribution of these depot fats. However, Pitts[122] did report that the fat content of the liver, spleen, and central nervous system of the guinea pig was relatively uniform when diets containing 5 to 50 per cent of fat were given; on the other hand, the fat content of the heart, kidney, muscle, gut, bone, skin and adipose tissue was directly proportional to the total body fat which, in turn, varied with the fat intake. The skin lipids were found to be most sensitive to changes in total body fat.

The type of fat laid down in the several fat depots of any one species is essentially uniform although, in general, the omental fat is usually slightly more saturated than the depot fat in other sites.

The composition of the body fat has long been known to be markedly influenced by the dietary fat, particularly when fat comprises a large proportion of the diet. Thus, in the classical experiments of Lebedeff,[123] it was found that the fat obtained from a dog which had been fed linseed oil had an abnormally low melting point and a high iodine number. After mutton tallow was given, it was observed that the depot fat was abnormally hard, and melted above 50° C. This fat was "almost identical with mutton tallow." Another similar demonstration was that of Munk,[124] who reported that the fat of dogs fed on generous amounts of rapeseed oil contained a large proportion of erucic acid, an acid never found under normal conditions in the depot fat of these animals. Erucic acid is the principal fatty acid present in rapeseed oil.

Animals cannot deposit the short-chain acids, acetic, butyric, caproic or caprylic acid. However, when the 10-carbon acid, capric, or the 12-carbon acid, lauric, is given, considerable amounts of these are deposited. Most odd-chain acids, likewise, are incapable of storage in the tissues although, oddly enough, Visscher[125] did find a considerable quantity of the 11-carbon acid, undecylic, in the body fat of rats which had been fed on triundecylin over a period of six weeks.

The composition of fat in the fat depots is extraordinarily sensitive to

dietary unsaturated fatty acids Thus the proportion of linoleic and linolenic acids laid down in these fat depots is largely a function of their content in the diet The failure to realize this fact was largely responsible for the so-called 'soft-pork problem,' which was a common one in this country during the twenties The fat from hogs previously receiving large proportions of peanuts or soybeans was so soft that slabs of bacon were flaccid shapeless and almost impossible to handle in extreme cases the meat cuts were practically unsaleable The soft lard was directly traceable to the presence of large quantities of linoleic acid A proportion of this acid as high as 30 per cent was noted in contradistinction to a normal content of 1 9 per cent for the acid on the usual diets The cause of the production of soft pork as well as the method for preventing it, have been largely worked out by Ellis and co-workers[126–129]

A number of factors tend to produce a hardening effect on adipose tissue Thus, cottonseed oil was shown to exert this effect, in spite of its high content of linoleate It is believed that the stearic acid present in this triglyceride may be the factor responsible for the hardening effect The most pronounced hardening agent has been shown to be carbohydrate[127] Fat from animals on a fat-low diet which is also high in carbohydrate has been shown to have a relatively high melting point and a low linoleate content It was found that the character of the fat on hogs could be changed from the soft type occurring after the peanut or soybean diet to a hard one by maintaining the animals on a high carbohydrate diet for several months

Other Factors Influencing Body Fat —Environmental temperature is one factor which influences the properties of the depot fat Thus when the environmental temperature is high, the tendency is to produce a fat melting at a higher temperature and having a lower iodine number than occurs when the outside temperature is moderate Conversely when animals are exposed to a very cold temperature they lay down more liquid fats having a lower melting point and a higher iodine number than would otherwise be the case

The hormone thyroxine has a powerful effect on the quantity of depot fat In spite of the fact that the total fat may be reduced as much as 50 per cent by the administration of the thyroid hormone no variation in distribution could be observed[130] Apparently all fat depots are equally affected The iodine number of the fat laid down in rats receiving thyroxine was higher than that present in the control animals hereby indicating a greater synthesis of unsaturated acids or a more extensive destruction of the saturated ones when thyroxine was given

Abnormal Fat Storage

Two different types of abnormal lipid storage are well recognized In the first case greater than normal amounts of fats are stored in the usual fat depots with the result that obesity or adiposity occurs Under such conditions the fat deposits consist entirely of triglyceride fats In another type of abnormal lipid deposit the fatty material is deposited chiefly in organs such as the liver or spleen with the result that the affected organs may be considerably enlarged and their function may be markedly im-

pared The lipid materials deposited do not involve triglyceride fat but rather cholesterol phospholipids, or even cerebrosides

Abnormal Deposition of Tryglyceride Fats —(*a*) *Ordinary Types of Obesity* —Newburgh,[131] in his review on obesity, defines obesity as the condition in which the body contains an abnormally large amount of adipose tissue Conn[13] also reviewed this subject Excess adipose tissue may be evenly distributed or it may be localized in discrete encapsulated masses, this condition is referred to as *lipomatosis* Although there are many theories to explain obesity, all investigators agree that this condition can occur only when the ingested calories exceed those which are expended

(*b*) *Abnormal Deposition of Triglycerides in the Liver* —Peters and Van Slyke[119] classified fatty livers into physiologic and pathologic In the physiologic type, which develops whenever large amounts of fat are mobilized from fat depots to meet unusual requirements for fat oxidation, the normal proportion of the several lipid components is not altered Physiologic fatty livers occur in fasting, in carbohydrate starvation, and in pancreatic diabetes

On the other hand, the pathologic type of fatty livers results from a dietary disorder, or from injury to the liver tissue which results in retardation of the lipid turnover The extent of fatty infiltration is greatly exaggerated in the pathologic type as contrasted with the physiologic fatty livers moreover, the normal proportion of the several lipids found in pathologic fatty livers may differ greatly from the normal pattern

The most important factor concerned with the development of the dietary type of fatty livers is choline It is now known not only that choline or the closely related betaine will inhibit the development of such fatty livers, but that compounds which function in the *in vivo* synthesis of choline are also of importance in preventing this condition The amino acid, methionine, is probably the most important in this respect, by virtue of its ability to transfer its methyl group to ethanolamine and so bring about the synthesis of choline Conversely, fatty livers may result on marginal diets when compounds having a higher priority for methyl groups than does ethanolamine are present to deplete the supply of methyl groups The amount of fat deposited in the liver of rats fed a choline deficient and protein deficient diet is influenced by the type of dietary fat, the ingestion of saturated fatty acids seems to aggravate the fatty liver condition[139a] Fatty livers may also be attributable to a deficiency of the essential fatty acids, due to the failure in phospholipid synthesis It has recently been reported[108] that an abnormal accumulation of cholesterol occurs in the liver in essential fatty acid deficiency When animals are poisoned by chloroform, carbon tetrachloride, phosphorus, or hydrazine, an intense fatty infiltration occurs

Various Types of Lipidoses —In some cases, an abnormal deposition of lipids other than triglycerides may occur Thannhauser[133] coined the term *lipidoses* (also spelled lipoidoses) to designate a group of diseases in which lipid deposition occurs in the reticulum and histiocytes A number of these conditions are described below

(*a*) *Xanthomatoses* —In the diseases included in this category, cholesterol esters are present in large proportion, while the neutral fats are of less importance In the primary type of xanthomatosis, fatty deposits may

occur on the eyelids, on the tendons or in the blood vessels or endocardium. In a secondary class of primary xanthomatosis, the type in which skin xanthomas occur is probably the most common. The well known Schuller-Christian syndrome belongs in this subdivision of xanthomatosis. The so-called secondary xanthomatosis is another main group in which the xanthomatosis is secondary to another disease characterized by hyperlipemia, such as diabetes.

(b) *Niemann-Pick's Disease*.—This disease, also called reticular and histiocytic sphingomyelinosis, first discovered in 1914, is a familial condition, in which there are unusually large deposits of the phospholipid sphingomyelin.[134] This phospholipid not only fills the cells of the reticulo-endothelial system, but it is present in excess in all organs.

(c) *Tay-Sachs' Disease*.—In 1896 Sachs[135] first described this disease which was defined as a "family form of idiocy, generally fatal, associated with early blindness." It was discovered by Klenk[136] and by Klenk and Langerbeins[137] that a new group of lipids, first identified as "Substance X" and later known as "gangliosides," were present in excess in the brain in this type of lipidosis.

(d) *Gaucher's Disease*.—This disease is also referred to as reticular and histiocytic cerebrosidosis. An enlargement of the spleen occurs; the liver and osseous system are involved, and the lymph nodes are also affected. In this condition an excess of cerebroside is deposited in the spleen, with the result that a marked enlargement of this organ ordinarily occurs. Considerable amounts of cerebrosides are likewise present in the liver. The cerebrosides deposited in the spleen usually contain glucose in place of galactose, although some of the latter type are present. There is no evidence that the brain cerebrosides of patients having Gaucher's disease vary from the normal galactose-containing type.

SYNTHESIS OF FATS AND OF OTHER LIPIDS IN THE ANIMAL BODY

Synthesis of Fat

Experimental Proof of the Synthesis of Fat.—(a) *Synthesis from Carbohydrate*.—It has long been recognized that fats can be synthesized in the animal body from non-fat precursors. As early as 1883 Meissl and Strohmer[138] proved by balance experiments that carbohydrate is converted to fat in the hog. Their proof was based upon the fact that the carbon in the ingested rice starch could not be wholly accounted for in the excreta (urine, feces, expired air) and body glycogen; the only conclusion possible was that the missing carbohydrate carbon must have been converted to fat. Similar experimental data were later reported for the goose[139] and for the dog.

A second general procedure for demonstrating the transformation of carbohydrate to fat involves the study of the changes in the R.Q. (Respiratory Quotient) during fat synthesis. The R.Q. represents the proportion between the volumes of respiratory CO_2 excreted and the volumes of respiratory O_2 absorbed. When carbohydrate alone is being oxidized the

R.Q. is 1.00. However, when relatively oxygen-rich carbohydrate is being converted to relatively oxygen-poor fat, less oxygen is required, and the R.Q. may approach a theoretical maximum of 8.00. In practice, an R.Q. as high as 1.33 has been recorded for a goose stuffed with carbohydrate, as compared with a fasting R.Q. of 0.73 in this animal. Figures of 1.39 have been reported for the R.Q. of the marmot prior to hibernation,[140] while Wierzuchowski and Ling[141] cited an average value of 1.40 for the R.Q. of a young pig over a twenty-hour period, after starch and glucose feeding, with a maximum figure of 1.58. The maximum fat production from carbohydrate was calculated at 7.1 gm. per hour, and 125 gm. per day. Under these unusual conditions, only 27 per cent of the metabolized carbohydrate was used for basal metabolism, 13 per cent was required to satisfy the specific dynamic action, while the remaining 56 per cent of the glucose obtained from the starch was converted to fat.

(*b*) *Synthesis from Protein.*—Since protein can be transformed to carbohydrate, it is only logical to assume that this newly-formed carbohydrate can give rise to fat. Cremer[142] was able to demonstrate the conversion of protein in lean meat to fat in a fasted cat, using the balance type of experiment. The same demonstration was made by Atkinson, Rapport, and Lusk,[143] who used the R.Q. as a criterion. When large amounts of proteins were fed to a dog whose tissues were completely charged with glycogen, considerable of the carbon was retained in a non-protein form. Since the R.Q. observed was higher than that occurring when protein is completely metabolized, it was concluded that the R.Q. of the retained moiety was less than that of carbohydrate, and, in fact, represented a storage of fat.

The Mechanism of Synthesis of the Saturated Fatty Acids.—The fact that a preponderance of all natural fats are composed of fatty acids with an even number of carbon atoms would seem to be convincing evidence that they are synthesized by the condensation of an intermediate containing an even number of carbon atoms. Since, in the case of butter, all even-numbered carbon acids occur, from butyric (C_4) to arachidic (C_{20}) acid, in which differences are stepwise and amount to 2 carbon atoms each, it is only natural to postulate that a 2-carbon compound forms the building stone for this synthesis. This hypothesis was suggested by Raper[144] as early as 1907.

(*a*) *The Nature of the 2-Carbon Building Stone.*—It is now believed that acetate or some acetic acid derivative functions as the active intermediate in fat synthesis. In addition to proof obtained with yeast and with bacteria, animal experiments have furnished evidence of the synthesis of fatty acids from acetate. Thus, Rittenberg and Bloch[145] proved that, after the feeding of $CD_3C^{13}OOH$ to mice, both deuterium and C^{13} were present in the newly-synthesized fat. Approximately 50 per cent of the carbons were of the C^{13}-variety, indicating the presence of both acetate carbons in the fat molecules. It was later shown by Rittenberg and Bloch[145] that long-chain fatty acids synthesized by mice and rats after the feeding of carboxyl-labeled acetate, had the label uniformly distributed throughout the molecule. A similar result obtained when liver slices were incubated with labeled acetate.[146] After the injection of carboxyl-labeled acetic acid

into goats, it was found that C^{14} was present exclusively on carbons 1, 3, 5 and 7, and was entirely absent from carbons 2, 4, 6 and 8. These and other supporting data indicate that the synthesis of the long-chain acids results from successive additions of acetic acid through the methyl group to the carboxyl group of the partly synthesized acids.[147] James *et al.*[147a] have recently reported the synthesis of odd chain fatty acids by the addition of the C_2 unit to propionic acid, through a mechanism similar to that obtaining for the synthesis of even-membered fatty acids.

(*b*) *The Rôle of Coenzyme A in Fat Synthesis.*—It is believed that an "active acetate" is formed by the combination of the acetyl group with Coenzyme A (Co A) to give the reactive acetyl Co A, as postulated by Lipmann.[148]

(*c*) *The Site of Synthesis of Fats.*—The liver has long been recognized to be one of the chief sites for the synthesis of fats. The lactating mammary gland, particularly in the case of ruminants, may function extremely effectively in promoting the synthesis of the fat excreted in the milk. Apparently fat synthesis may be effected with even greater facility in the ruminant mammary gland than in the liver, inasmuch as slices of the mammary gland are able to produce a direct synthesis of fat from acetate,[149] while in liver slices, fat cannot be produced from acetate unless glucose is also present.[150] The demonstration that the volatile fatty acids, as well as the long-chain acids, in milk fat owe their origin to a direct synthesis in the udder from acetate present in the plasma has completely revolutionized our concept as to the source of milk fat. The short-chain acids are no longer believed to originate as degradation products of serum oleic acid.

In addition to the liver and mammary gland, many other tissues, such as the kidney, diaphragm, mucosa of the gastrointestinal tract, lung, and even the arterial wall, are capable of forming fatty acids from acetate. Apparently most tissues possess the ability to effect this fat formation. It is of especial interest that the synthesis of fat is likewise a function of the adipose tissue itself.[151] The subject of synthesis of fatty acids and fat from acetate has been reviewed by Popják[152] and by Folley.[153]

Fatty acid synthesis has been achieved in liver slices, liver homogenates and in water soluble systems. It was formerly thought that the synthesis of fatty acids was the reverse of fatty acid oxidation. However, evidence has been accumulating which has resulted in at least a partial separation of the two pathways. Whereas all the enzymes responsible for fatty acid oxidation are contained in the mitochondria of the cells, fatty acid synthesis requires the simultaneous presence of an extra mitochondrial enzyme (probably present in microsomes). A requirement for reduced triphosphopyridine nucleotide (TPNH) in fatty acid synthesis has also been reported.[153b]

The Synthesis of Unsaturated Fatty Acids.—According to the theory of Leathes and Meyer-Wedell[154] desaturation is the first step in fatty acid catabolism. It would therefore be expected that unsaturated fatty acids could be formed *in vivo* from the corresponding saturated acids. Schoenheimer and Rittenberg[155] using isotopically labeled saturated fatty acids demonstrated their conversion to unsaturated acids. It has been shown that oleic acid can originate from stearic acid, and that palmitoleic acid can be formed from palmitic acid.

Although the monoethenoid acids can be synthesized in the animal body, the ability of the animal to form polyunsaturated fatty acids from these or other sources is under investigation Bernhard and Schoenheimer[156] convincingly proved that neither the diethenoid acid, linoleic, or the triethenoid acid, linolenic, was produced in the rat from carbohydrate, although large amounts of palmitic and stearic acid were formed from this foodstuff James and coworkers[156a] have recently reported that human blood cells can synthesize linoleic and arachidonic acids, although rat red cells are unable to do so The tetraenoic essential fatty acid, arachidonic, can be built up in the mouse by the addition of acetate to linoleic acid [157]

The Synthesis of Glycerol —The conversion of glycerol into glucose has been repeatedly demonstrated in the intact animal, this reaction can also *proceed in the reverse direction* Although mammary tissue has been shown to effect the synthesis of glycerol from acetate, this process is apparently not a direct one, as the synthesis cannot be mediated in slices of this gland The increased fat synthesis which has been demonstrated on the addition of glucose and insulin to mammary tissue is not believed to be attributable to the glycerol which is thus made available [158]

The Synthesis of Phospholipids

Phospholipids can readily be synthesized by all animals Animals develop normally and their tissues contain the normal quota of phospholipids even when no phospholipids are present in the diet, and all phosphorus is given in inorganic form

The liver has long been considered to be the principal organ in which phospholipid synthesis takes place The biological synthesis of the phospholipid, lecithin, in liver is accomplished through the combination of D-α,β diglycerides and cytidine diphosphate choline [158a] Probably the second most important site of phospholipid synthesis is the small intestine Another important tissue in which phospholipids can be produced in the kidney Slower rates of synthesis of phospholipids obtain in muscle and brain According to Hevesy and Aten[159] and Artom,[160] newly-formed phospholipid of blood plasma is actually produced in the liver The rate of synthesis of choline phospholipids is stimulated by choline itself, *ethanolamine* augments the synthesis of both the ethanolamine and the choline type of phospholipids Phospholipid synthesis is increased by pancreatectomy

The Synthesis of Cholesterol

Cholesterol can be completely synthesized in the animal body Several investigators proved that acetate is the raw material employed in preference to other metabolites in the animal organism [161] Both carbon atoms of acetate contribute to the cholesterol molecule The mechanism involved in the biosynthesis of cholesterol from acetate involves the conversion of acetate to squalene, probably through the precursor, mevalonic acid, the cyclization of squalene to lanosterol, and the demethylation of lanosterol to yield cholesterol Popjak[16] has recently reviewed *the subject of the* biosynthesis of cholesterol

THE OXIDATION OF FATS IN THE ANIMAL BODY

Theories on the Oxidation of Fats

The metabolism of the glycerol and fatty acid moieties of fat are believed to follow entirely independent courses. It is generally believed that glycerol is converted to glucose and that its eventual metabolism becomes merged with that of the monosaccharide. Several theories have been advanced to explain the intermediary metabolism of the fatty acid moiety. The present theory for the mechanism of fatty acid oxidation is a combination of several of these hypotheses.

The β Oxidation Theory.—According to this theory fatty acids are oxidized on the β-carbon atom, *i.e.*, on the second carbon from the carboxyl group. A 2-carbon fragment, presumably acetic acid, is split off from this β-keto-acid and a new fatty acid containing 2 carbons less than the original fatty acid is then ready to be subjected to a new β-oxidation. This oxidation cycle continues until the long chain fatty acid has been degraded into a number of acetic acid fragments. In some cases oxidation is partially inhibited at the stage of the 4-carbon acid under these conditions the ketone body acids, acetoacetic ($CH_3 \cdot CO \cdot CH_2 \cdot COOH$) and β-hydroxybutyric ($CH_3 \cdot CHOH \cdot CH_2 \cdot COOH$) accumulate in the tissues. These acids together with the related product, acetone, $CH_3 \cdot CO \cdot CH_3$, are referred to by the connotation acetone or ketone bodies.

Multiple Alternate Oxidation.—Jowett and Quastel[163] proposed the multiple alternate oxidation theory to explain the fact that caprylic and capric acids yield more than one ketone body per molecule. According to this hypothesis, fatty acids are oxidized simultaneously at alternate carbon atoms in contradistinction to the stepwise procedure in the original β oxidation theory. Although the multiple alternate oxidation theory is an attractive one, it lacks experimental confirmation. Moreover, the presence of such polyketones has not been demonstrated.

The β Oxidation Acetic Acid Condensation Theory.—According to this theory, the breakdown of fatty acids proceeds by β-oxidation, while the acetic acids so liberated are free to recondense to acetoacetate.[164] However, the quantitative relations of the ketonuria after caproic and sorbic acid administration do not fit in with this theory.

The ω Oxidation Theory.—Verkade and van der Lee[165] reported that fatty acids of medium chain length may be oxidized at the ω-carbon that is on the carbon atom farthest from the carboxyl group. The principal fatty acids which follow this pathway of oxidation in man are capric (decanoic) and undecanoic, while lauric (dodecanoic) acid gives rise only to traces of dicarboxylic acid and tridecanoic acid has no diacidogenic properties. Although this alternative pathway is available for the medium-length fatty acids, it is believed that the β-oxidation mechanism is important for these acids also. From a quantitative standpoint ω-oxidation apparently plays an extremely minor role in fatty acid breakdown.

The Dehydrogenation Theory.—Leathes and Raper[166] advanced the hypothesis many years ago that the first step in oxidation of fatty acids involves their desaturation in the liver. It has been suggested that α,β-

desaturation precedes the formation of the β keto acids 9,10-Dehydrogenation offers an explanation of the mechanism by which oleic acid can be formed from stearic acid The relationship between dehydrogenation and oxidation of fatty acids has been reviewed by Breusch[167]

Enzyme Systems Involved in Fat Oxidation

The oxidation of fatty acids probably takes place exclusively in the mitochondria of the intact cell The major site of fatty acid oxidation is the liver

I *Activation Enzymes* —These catalyze the formation of acyl CoA from the free fatty acid with the concomitant change ATP (Adenosine triphosphate) → AMP (Adenosine monophosphate) + pyrophosphate At least 3 different enzymes, called thiokinases, having various ranges of specificity cover the gamut from C_4 to C_{18}

II *Fatty Acid Dehydrogenases* These catalyze the dehydrogenation of fatty acyl-CoA in the α, β position The dehydrogenases involved here contain a FAD (flavine-adenine dinucleotide) prosthetic group

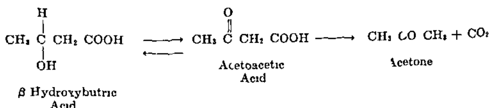
III *Fatty Acid Hydrases* These catalyze the reaction of unsaturated fatty acyl-CoA to β-hydroxyl acyl CoA

IV *Fatty Acid Oxidases* These catalyze the reaction β hydroxyl acyl CoA to β-keto acyl-CoA These dehydrogenases contain DPN (diphosphopyridinenucleotide) as the primary electron acceptor

V *Cleavage Enzymes* —These enzymes ("thiolases") bring about the change of β-ketoacyl-CoA to acetyl- CoA and acyl-CoA The latter compound contains 2 less carbons than does its parent keto-compound As soon as acetoacetyl CoA is formed, the reaction may be terminated in either of the following ways (*a*) By enzymatic deacylation of acetoacetyl CoA to acetoacetate, (*b*) by cleavage of acetoacetyl-CoA to 2 molecules of acetyl CoA by their condensation with oxaloacetate Lynen[168] and Kennedy[168] have recently reviewed the subject of fatty acid oxidation

Ketone Body Metabolism and Fatty Acid Oxidation

Introduction — The ketone bodies (acetone bodies) are intermediates in the oxidation of fatty acids The 3 components which comprise this group of compounds are related to each other as follows



Whenever large amounts of fat are being metabolized in the absence of carbohydrate the amount of ketone bodies in the blood rises so that a *ketosis* ensues, and these substances are excreted in the urine *i e* a *ketonuria* or an *acetonuria* is present Small amounts of ketone bodies are be-

lieved to occur normally in the body as intermediates of the fatty acids. However, under normal conditions, the acetoacetate is believed to be either directly oxidized to carbon dioxide and water after incorporation into the Krebs cycle or converted to 2 molecules of acetate which are oxidized *via* the Krebs cycle.

Conditions Resulting in Ketonuria.—Ketonuria results under both physiologic and pathologic conditions. Prior to the advent of insulin, ketosis was a constant concomitant of diabetes mellitus. Frequently, the extreme acidosis engendered in this condition was at least partially responsible for the fatal outcome of this disease. The acidosis occurs because of the depletion of the alkali reserve of the blood as a result of the urinary excretion of the ketone body acids as their salts. This type of acidosis is usually referred to as a ketosis. Excretion of ketone bodies in quantities in excess of 100 gm daily have been observed by several investigators in diabetics. Ketonuria likewise results in experimental types of diabetes such as pancreatic alloxan and phlorhizin diabetes although the severity of the condition in dogs is generally less than is the case with the disease in human subjects.

Fasting is the most common physiologic condition in which a ketonuria develops. The rate of development and the intensity of the ketosis vary with species. A high level of ketonuria obtains under such conditions in man, as well as in the higher apes and in monkeys. The ketonuria which results in dogs, rats, steers, goats and rabbits on fasting reaches only a low level although conditions exist in which a ketonuria of greater magnitude may occur in this group. The most complete review on the subject of ketosis in domestic animals is that of Sampson.[169]

A considerable degree of ketonuria also results in man when he subsists on a protein fat diet. Thus McClellan and DuBois[170] and Tolstoi[171] reported the occurrence of a ketonuria which persisted continuously over a year during which 2 Arctic explorers were ingesting a high protein-fat carbohydrate low diet.

Sources of Ketone Bodies.—Ketone bodies originate from the *in vivo* oxidation of all saturated straight-chain acids having an even number of carbons from butyric (C_4) to stearic (C_{18}).[17] On the other hand odd-chain carbon acids from C_3 to C_{11} were found to be almost completely ineffective in producing ketonuria[172] although it has been reported that a moderate ketonemia occurs after these acids have been fed.[173,174] Ketone bodies also originate by the condensation of acetic acid molecules.[174] Unsaturated fatty acids such as crotonic (C_4), vinyl acetate (C_4), and sorbic acid are likewise sources of ketone bodies.[175]

In addition to the fatty acids certain amino acids are ketogenic. Leucine is a potent source of acetone bodies while isoleucine is believed to be the source of both acetone bodies and glucose.[176] Although it has been generally considered that phenylalanine and tyrosine are likewise ketogenic later investigations have given conflicting results. Isotope studies suggested that the α and β-carbons of tyrosine become the carboxyl and α-carbon of acetoacetate.[177]

Factors Altering the Extent of Ketonuria.—As mentioned earlier, species is an important factor in determining the extent of ketonuria during

fasting. Man, higher apes, and monkeys are the most susceptible to this condition, while most of the domestic and laboratory animals are quite resistant to the development of a ketonuria. However, in recent years, a high degree of ketonuria has been demonstrated in cattle, sheep, goats, and sows during pregnancy.

Age is another factor which has generally been considered to be closely related to the severity of ketosis. According to Peters and Van Slyke[118] and Heckscher,[178] starvation ketosis appears earlier and reaches higher maxima in infants and in children than it does in older individuals.

Sex is one of the conditions which most profoundly affects the level of fasting ketonuria. Deuel and Gulick[179] reported that the level of ketonuria in normal fasting women was approximately 5 times that in normal fasting men, when compared on the surface area basis. The general nature of this sex difference is evident from the fact that it has been shown to occur in the exogenous ketonuria of rats and guinea pigs, and in the endogenous ketonuria of rats. It is believed that the high level of ketonuria in the female reflects a different type of fat and carbohydrate metabolism in this sex. Other related evidences of a sex difference in fat metabolism are the high level of liver fat and storage (particularly subcutaneous) fat, and conversely the lower value for liver glycogen in the female as contrasted with the male.

A number of hormones have a considerable effect in altering the degree of ketonuria. The most important of the endocrine organs, other than the sex glands, is the anterior lobe of the pituitary gland. The active principle is often referred to as the "ketogenic" or "diabetogenic" hormone. The injection of such extracts produces a fatty infiltration of the liver, and a retardation in the oxidation of carbohydrate. However, the ketogenic hormone is able to effect a ketonuria only in fasted rats, while it is ineffective in fed animals. On the other hand, hypophysectomy abolishes the occurrence of fatty livers even after the administration of powerful hepatotoxic agents such as carbon tetrachloride. It is thought that the reduced ketonuria in hypophysectomized animals may be accounted for on the basis of reduced activity of the thyroid gland.

The level of various types of ketonuria is markedly reduced by total adrenalectomy. On the other hand, the injection of ACTH or of cortisone has been shown to induce a partial or complete suppression of hyperketonuria or ketonemia induced by fasting. It is suggested that this may be attributable to the increased rate of ketone body utilization by peripheral tissues, or by the decreased rate of ketogenesis.

The Mechanism by Which Carbohydrate Reduces Ketonuria.—The interrelationship between carbohydrate and fat metabolism is illustrated most dramatically by the striking effects exerted by small amounts of carbohydrate on fasting ketonuria, or on that induced by a protein-fat diet. In fact, one of the familiar aphorisms in the earlier literature is that of Rosenfeld,[180] which states that "Fat burns in the flame of carbohydrates." The subject of the interrelationship of ketosis and carbohydrate metabolism has been reviewed by Deuel and Morehouse[181] as well as by Stadie.[18]

Two main concepts have been cited to explain the effect of carbohydrate

on ketosis In the first place it was believed that a coupled reaction occurs between glucose or some carbohydrate intermediate and acetoacetate which enables the latter molecules to be oxidized simultaneously The compound which presumably combines with the acetoacetate is spoken of as being *ketolytic*, while this theory is referred to as the *ketolysis* theory The hypothesis that a quantitative relationship obtains between the ketogenic and the ketolytic (or antiketogenic) molecules, which was beautifully worked out by Shaffer[183] has not been widely accepted during the last few years However more recent work has demonstrated that oxaloacetate (from carbohydrate) combines with acetic acid (from acetoacetate), thus bringing the latter into the tricarboxylic or citric acid cycle The same system operates not only with acetoacetate but also with the 2-carbon fragments formed by the oxidation of longer aliphatic fatty acids When large amounts of carbohydrate are available the citric acid cycle operates at a high level and ketone bodies readily become incorporated into it with the result that no appreciable ketonuria is present On the other hand when carbohydrate is present only in minimal quantities, the citric acid cycle operates at such a low level that it is unable to bring about the oxidation of all the ketone bodies, and they accumulate in the blood and tissues If one accepts this hypothesis, it is evident that a semiquantitative relationship does obtain between the level of carbohydrate and that of the ketogenic material present

The so-called antiketogenesis theory postulates that carbohydrate is preferentially oxidized in the animal body and that, whenever carbohydrate is available for oxidation, the oxidation of fat is suppressed so that the ketone bodies produced by the liver do not exceed the capacity of the liver to oxidize them If this concept were correct there would be no direct relationship between the oxidation of carbohydrate and that of acetoacetate Although much experimental evidence favors the ketolysis theory Lossow and Chaikoff[183a] have recently reported that carbohydrate spared fat oxidation by depressing the breakdown of palmitate

(a) *The Comparative Ketolytic Effect of the Sugars* —It has generally been considered that the ketolytic effect of sugars and of glucose intermediates would be in proportion to the D glucose which can be derived from the compound in question This supposition, however does not fit in with the finding that D galactose is superior to glucose as a ketolytic agent as demonstrated both in the ketonuria induced by fasting in man and in that occurring on a protein fat diet[184] Moreover a similar variation between galactose and glucose has been shown to obtain in the exogenous ketonuria of rats[185] It has been reported that the glycogen formed from galactose although quantitatively of a lower order than that formed from glucose is retained for a longer interval of fasting than is that which is produced after the administration of glucose It would thus appear that the effectiveness of ketolytic substances in preventing ketonuria is related to the glycogenic action of the substance in question There is some evidence that fructose and sucrose exhibit a somewhat more pronounced ketolytic effect on ketonuria in man than does glucose[184] while lactose was found to have an intermediate position between galactose and glucose in the rat[186]

Intermediary Metabolism of Fatty Acids Other Than Through the Ketone Bodies

Acetic Acid and the Acetyl Group.—Acetic acid plays a key rôle in the metabolic processes of the animal body. On the one hand it serves as the building stone in the synthesis of fatty acids, and on the other hand it is also the fragment formed from fatty acids as a result of β-oxidation. Acetic acid may be converted to acetoacetate, or it may combine with oxaloacetate and participate in the citric acid cycle.

In addition to all of the above important functions, which have been reviewed earlier, acetic acid serves as a building stone for the steroid nucleus, as well as for that of porphyrin and of uric acid. Probably the most important function which acetic acid exerts is in the acetylation reaction, whereby it reduces the toxicity and the physiologic action of the amines by combining with the latter as the acetyl group. The metabolism of acetic acid was comprehensively reviewed by Bloch.[186]

Formic Acid and the Formyl Group.—Practically nothing was known of the metabolism or of the metabolic significance of formic acid before the advent of isotopic technics. It is now known that the "formyl" group, the 1-carbon fragment, behaves in a manner analogous to that of the "acetyl" group. In order to undergo the several reactions formate must be present in the form of "active formate", the so-called *citrovorum factor* (CF) is believed to be involved in the active formyl group.

Formate has been shown to participate in a number of syntheses which include the ureide carbons 2 and 8 of both uric acid and inosine-5-phosphate. Formate carbon is likewise the precursor of the methyl group in thymine and of the β-carbon of serine. According to Sakami and Welch,[187] the labile methyl group which is concerned in the synthesis of methionine and choline can originate from formate. The carbon of formate is also involved in the synthesis of heme; it has been reported that folic acid is concerned with this particular reaction.[188]

Formate as such does not ordinarily occur in our foods. However, this molecule originates in the metabolism of a number of compounds, including histidine (2-carbon on pyrrol ring), acetone, threonine (2-carbon). Glycine, methionine, and tryptophane also may contribute to the active formyl group. Welch and Nichol[189] reviewed the reactions of formate.

Odd Chain Fatty Acids.—Odd chain fatty acids are oxidized similarly to the even-numbered compounds by essentially the same enzyme systems. The removal of C units from an odd-unumbered fatty acid ultimately results in the formation of propionyl CoA (CH_3CH CO-CoA) which can yield propionic acid. Propionic acid can be further oxidized in the liver. Odd chain fatty acids can also be oxidized to form acetyl-CoA and acetoacetic acid.

Branched-chain Acids.—The metabolism of the branched chain acids differs in all cases from that of the straight-chain acids. In some cases, branched-chain acids may be entirely incapable of oxidation, under these conditions they may be detoxicated with glycuronic acid and excreted as such. The ability of such branched-chain acids to be metabolized depends to some extent upon the location of the side chain, and especially upon the

size of this side chain. According to Carter,[190] when the α-substituted group is larger than a methyl group, steric hindrance occurs which prevents the enzymatic attack on the carbon chain. Carter[190] contributed an excellent review on the metabolism of branched-chain acids.

INTERMEDIARY METABOLISM OF CHOLESTEROL

The metabolic changes of phospholipids and cholesterol are of especial interest in the nutritional evaluation of fats. The intermediate changes which occur in the case of phospholipids are similar to those of the neutral fats, and therefore they will not be considered here.

As has already been discussed earlier, cholesterol is readily synthesized in the body from the 2-carbon molecule, acetate. All substances which can yield acetate therefore become precursors of cholesterol. Presumably this includes not only the fatty acids but also ethyl alcohol, alanine and a number of other amino acids which can yield acetate directly via pyruvic acid or indirectly by way of glycogen, glucose and pyruvic acid. The conversion of such compounds to fat, with a resultant formation of acetate on oxidation of the fatty acids, offers another possible route for the production of acetate. Carbohydrates also may furnish acetate directly via pyruvic acid or indirectly after being converted to fat. Thus practically every foodstuff becomes a possible source of acetate and hence of cholesterol. According to Alfin-Slater and co-workers,[191] the rate of synthesis of cholesterol in the rat was uniform irrespective of whether a fat-free diet was fed or one containing 30 per cent of fat.

Many tissues have the capacity to effect the synthesis of cholesterol. It is pretty generally accepted that the liver is the principal organ which carries out the synthesis; the skin has also been found to possess this capacity to a high degree. The adrenal cortex, kidney and lung are also sites for cholesterol synthesis. In fact, it has recently been demonstrated that in cattle cholesterol can be produced from acetate even in the walls of the aorta. It is not certain to what extent these findings are applicable to man.

Under ordinary conditions cholesterol is maintained at a uniform level in the tissues despite variations in intake. The uniformity in composition is controlled by balancing the quantity absorbed and synthesized with the amount destroyed, excreted as such, or transformed to other compounds.

The most important biologic function of cholesterol is as the mother substance of hormones. Thus Bloch[192] proved that cholesterol is the precursor of the female sex hormone, pregnanediol. There is every indication that cholesterol is the source of the other sex hormones which possess the steroid nucleus, as well as of the adrenocortical hormones. In fact, the better survival of hyperthyroid rats on a high cholesterol diet, as contrasted with controls on a cholesterol-low regimen,[193] might be interpreted as related to the ability of the first group to maintain the adrenocortical hormones at a normal level in the blood and tissues in spite of their rapid turnover due to the action of the thyroid hormone. Cholesterol is likewise known to be the mother substance of 7-dehydrocholesterol which, in turn, is converted to vitamin D_3 after irradiation of the skin.

Excreted or unabsorbed cholesterol may undergo several transformations in the gastrointestinal tract, particularly in the large intestine. It may be reduced to dihydrocholesterol (cholestanol), or be converted to another compound, coprosterol (coprostanol), which is isomeric with dihydrocholesterol. In both cases, the new compounds result from the saturation of the cholesterol molecule, presumably due to the reducing action brought about by the intestinal bacteria. Coprosterol received its name because it is an invariable component of feces.

The most abundant end products of cholesterol metabolism in higher animals are the bile acids. The site of conversion of cholesterol to bile acids is the liver. Bile acids occur in bile conjugated with the amino acids glycine and taurine. These bile salts are very effective emulsifiers for fat and also promote intestinal absorption of lipids, including cholesterol. The subject of bile acid metabolism has been reviewed by Bergstrom and Borgstrom.[193a]

THE NUTRITIONAL VALUE OF FATS

Although fats have sometimes been considered to be optional constituents of the diet, there has been an increasing realization in recent years that they play an essential role in the metabolic processes of the body. Since the discovery by Burr and Burr[194] in 1929 of the necessity of certain polyunsaturated acids for growth and, in fact, for survival, it has become evident that the functions of these so-called essential acids are more widespread than was originally realized.

A number of general facts emphasize the importance of fat in the diet. In the first place, fat has the highest caloric density of any of the foodstuffs, namely 9.3 cal./gm., as contrasted with values of approximately 4.1 cal./gm. for protein and carbohydrate. Actually, the discrepancy in caloric value of fat-containing diets as contrasted with those high in protein or carbohydrate is greater than the ratio of 9.3 to 4.1, since the latter two foodstuffs are usually diluted with a considerable quantity of water, while fat is usually water-free. Fats are also carriers of fat-soluble vitamins. They also exert a thiamine-sparing action. Finally, fats are necessary to give palatability to the diet. According to Starling,[195] the reduced consumption of food in Great Britain during World War I was definitely associated with the low-fat regimen. The subject of the importance of fats in nutrition has been reviewed by Deuel.[196]

The increased nutritional value of diets containing generous amounts of fat has been demonstrated by a number of different indices. A greater sparing action is exerted on protein metabolism in rats during fasting when the previous regimen has been one exceedingly high in fat than when the diets were proportionally rich in protein or in carbohydrate.[197] It has also been demonstrated that the same "wear and tear" quota obtained in rats on a protein-free diet, irrespective of whether a fat-free, carbohydrate diet was given or one which contained 20 per cent of fat, when 100 per cent of the caloric requirement was fed. When the caloric intake of the protein-free diets was successively reduced from 100 per cent of the caloric requirement to 75, 50, or 25 per cent of the calories needed to maintain caloric

equilibrium,[198] the nitrogen minimum was much more effectively maintained on the fat diet than on the fat-free regimen. The studies of Schwimmer and McGavack[199] also indicate that fats exert an important protein-sparing action in the case of man. The only conditions under which a low nitrogen excretion could be maintained in human subjects on protein-free diets, given at considerably below the amount required for caloric equilibrium, was when the diets contained considerable quantities of fat.

The rate of growth is another index which has been employed in establishing the nutritional value of fats. Hoagland and Snider[200] and later Deuel *et al.*[201] reported that the best growth of rats was obtained on diets containing approximately 30 per cent by weight as fat. In experiments of Forbes and co-workers,[202] pair-fed rats fed on isocaloric diets containing 2, 5, 10, or 30 per cent of fat presented progressively increasing gains in weight, fat digestion and nitrogen retention as the proportion of fat was increased. As a partial explanation for the increasing efficiency of high-fat diets in promoting growth, as compared with low-fat regimens, it has been demonstrated that this foodstuff exerts a peculiar effect on the specific dynamic action of other foodstuffs. Forbes and Swift[203] found that, when generous amounts of fat were present in the diet, the specific dynamic action induced by protein and carbohydrates was markedly reduced, thereby decreasing the proportion of waste calories and at the same time increasing the efficiency of utilization of the total calories. This phenomenon has been referred to as "associative dynamic action." It is suggested that if this same phenomenon applies to man, the unpleasant consequences of specific dynamic action during hot weather can be partially overcome by increasing the proportion of fat consumed.

The age at which sexual maturity occurs in the female rat is also related to the fat content of the diet. There is likewise some indication, on the basis of rat studies, that high-fat diets are superior to low-fat regimens during pregnancy and lactation.[204] Moreover, work capacity has been shown by two different groups of investigators to be superior on a fat-containing diet to that on one which is fat-free.[197, 201]

Finally, survival time during fasting has provided an interesting index of nutritive value. Samuels and associates[197] demonstrated that the period over which rats survived a complete fast varied according to the previous diet. When the fast followed a diet which contained 80 per cent of fat, survival time was 18.3 ± 0.44 days; on the other hand, when the previous regimen had contained a similar proportion of carbohydrate or protein, the average survival period was found to be 15.5 ± 0.46 days and 10.2 ± 1.68 days, respectively. It was suggested that the rats on the high-fat diet developed a sparing action for liver glycogen;[205] moreover, it was likewise demonstrated that the rate at which glucose was oxidized by the isolated diaphragms from rats on the high-fat intake was only about one-half that of the diaphragms obtained from rats on a high-carbohydrate regimen.[206]

The Importance of Essential Fatty Acids

The so-called essential fatty acids are the polyunsaturated acids which are necessary for normal nutrition and which cannot be produced *de novo*

or are produced in insufficient amounts in the tissues Three acids are included in this category, namely, linoleic acid, which has 2 double bonds, linolenic acid which has 3 unsaturated linkages, and arachidonic acid which is a tetraenoic acid The first 2 acids are 18-carbon acids which are found in vegetable oils, while the last one has 20 carbons and is found exclusively in animal fats Oleic acid, which has only a single unsaturated bond, is not included in this group, since it can be readily synthesized in the tissues

When the essential acids are absent from the diet of young rats, they cease to grow in ten to twelve weeks and, at the same time, develop an eczematous condition of the skin and feet, together with a scaly tail Moreover, Cheng and associates [07] demonstrated that the protective effect against x-radiation injury in rats, which is conferred by fats, is to be traced to their essential acid content Linoleate and cottonseed oil were shown to prevent the development of capillary fragility in the skin of rats [208] Apparently, the presence of the essential acids is in some manner required for the maintenance of sound capillary walls Finally, it has been reported by Alfin-Slater *et al* [108] that, in the absence of fat in the diet, abnormally large amounts of cholesterol accumulate in the liver, as compared with the content in rats receiving 12 5 per cent of fat in the diet This occurs in spite of the fact that blood cholesterol is reduced to a figure considerably less than that which occurs on a normal diet It is believed that the essential fatty acids are necessary for the efficient transport and metabolism of cholesterol

Essential fatty acids have recently been implicated in the problem of atherosclerosis through their connection with some phases of cholesterol metabolism Whereas the presence of saturated fat in the diet of animals and humans has been reported to produce hypercholesterolemia, diets containing unsaturated oils which contain large proportions of essential fatty acids tend to decrease serum cholesterol levels [106a] Also, diets high in fats containing essential fatty acids lead to a prolonged blood clotting time and an increased fibrinolytic activity of the blood, whereas diets containing large amounts of saturated fat have the opposite effect

Recently, it has been shown that liver homogenates of essential fatty acid deficient rats had abnormal mitochondria, which reduced the efficiency of prosphorylation [208a]

It is not certain to what degree the results obtained with laboratory animals can be applied to the normal nutrition of man Symptoms similar to those induced in the rat have been noted in the mouse and the dog There are no definite indications that the essential acids are required by adult men, although von Groer[209] and Hansen[210] reported that infants kept on a low-fat diet developed eczema, and that this condition was readily cured by fat feeding Brown and Hansen [11] correlated the presence of eczema tial fatty acids in the blood of adult subjects with the presence of essential On the other hand, Brown and co-workers[21] were unable to provoke symptoms of fat deficiency in a normal male subject by maintaining him on a fat-free diet for six months although a 50 per cent reduction of blood linoleate and arachidonate obtained

The Optimum Level of Fat in the Diet

If one accepts the experiments on rats as applicable to human nutrition, one must conclude that fats are obligatory components of the diet. However, although the same qualitative relations in nutritional value of foodstuffs in the rat and in man may be accepted as the usual phenomena, it is less probable that one can place equal reliance on the relative quantitative aspects in nutrition in these different species. For this reason one cannot say with certainty that the optimum level of fat, postulated for the rat, *i.e.*, 30 per cent by weight, would likewise apply to man.

Another approach to the problem is the estimation based on the fat consumption of normal individuals. If entirely free choice were possible, without economic factors, customs and habits entering into the picture, such a calculation would be of considerable value. On this basis, Brandt[13] reported that the daily fat intake by the British increased from 99 gm. per day before World War I to 124 gm. daily by 1934. The latter figure corresponds to the fat consumption recorded for Americans and Germans at this time. Fat accounted for 30 per cent of the calories of the diet between 1926 and 1930. In sharp contrast to these figures, the Orientals have an extremely low fat intake. Brandt[213] stated that the intake of fat calories by the Japanese before World War II was 6 to 10 per cent of the total calories. Moreover, Shen[14] estimates that the southern Chinese soldiers in World War II subsisted on a diet in which fat made up only 3 per cent of the total calories. On the other hand, Howe[215] gives a figure of 40 per cent for the proportion of fat to total calories in the mess of the American soldiers. In a report of the Food and Nutrition Board[16] published recently, t is stated that although the consensus among nutritionists has been that he human diet should provide at least 25 per cent of its energy in the form f fat, there is no concrete evidence to substantiate this. In the United tates, a diet containing 40 per cent of the calories in the form of fat has ovided one of the best health patterns in the world. Attempts to corree high fat intakes with increased incidence of atherosclerosis and coronary artery disease have not been conclusive.

The questions of (1) what is the optimum intake of fat and (2) what constitutes the most favorable fatty acid mixtures have still not been resolved, although evidence is accumulating that certain highly unsaturated fatty acids may be essential in the diet.

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Chapter 9

Calcium, Phosphorus and Magnesium

By D M Hegsted

CALCIUM AND PHOSPHORUS

Calcium and phosphorus are usually considered together since they constitute the major part of the mineral content of the skeletal tissues Most of the body's calcium and phosphorus are in the bones and the ratio of one to the other while not entirely constant, is nearly so Appreciable losses or gains by the body of one of these elements may be expected to be reflected in similar changes in the other On the other hand there are numerous phosphorus compounds in the body whose principal function is not related to the skeletal tissues or to calcium metabolism No attempt has been made to consider such compounds in detail in this chapter since they are more conveniently discussed elsewhere

Attention is directed primarily toward an evaluation of the nutritional needs for calcium and phosphorus and the factors which influence these requirements More emphasis is given to calcium than to phosphorus since diets of human beings are often low in sources of calcium seldom in phosphorus sources It has often been said that in the diet of the United States population as a whole calcium is the nutrient most often low relative to requirements This statement rests entirely upon estimates of calcium need rather than clinical evidence

THE BONE SALTS

Over 99 per cent of the body calcium and between 70 and 80 per cent of the body phosphorus is contained in the skeletal tissues The high mineral content is largely responsible of course, for the rigidity and strength of the bones and teeth Numerous studies[1,2] indicate that the bone salt is a multiple apatite similar to CaF_2 $3Ca_3(PO_4)_2$ and $CaCO_3$ $3Ca_3(PO_4)_2$ The various ions and cations are arranged in this proportion in a definite crystal lattice Ions of similar size and charge are to a certain extent interchangeable Minor variations in bone composition as the result of dietary modifications are thus explained as is the deposition of strontium lead and other elements in bone The surface area of bone is enormous[3] and opportunity for physical adsorption on the surface is great This complicates studies on bone composition

The use of radioisotopes has demonstrated that bone, like most tissues, is in dynamic equilibrium with the constituents of the plasma and other tissues[4,5] It must be noted that the rate of exchange is much greater than the rate of deposition of new bone The appearance of isotopes such

as Ca^{45} and P^{32} in the bone in in vivo studies must not be interpreted as a measure of calcification or bone growth.

The bones constitute a mineral reserve which may be drawn upon in time of need. The more easily mobilized calcium is in the trabeculae, and this is of particular importance during lactation in mammals or during the egg-laying period in birds when calcium requirements are very high.

The hard tissues of the teeth, dentine and enamel, are metabolically more stable than the bones. Little if any calcium is lost from the molar teeth of rats fed a low calcium diet[7] and phosphorus turnover is slow.[8] At present no convincing studies are available to show that calcium and phosphorus intakes are of primary importance in the problem of dental caries.

BONE FORMATION

It is obvious that the nutritional requirements for calcium and phosphorus are related in the growing animal to the amount of bone formation. The mechanisms involved in calcification are little understood.[16,17] Bone growth is complicated[10,11] and it should be clear that growth and maintenance of normal bone function are not solely a matter of calcium and phosphorus metabolism. Illogical conclusions have been drawn from a failure to consider the many factors involved. Perhaps all nutrients involved in growth affect bone growth. Reference may be made in particular to the effects of vitamin A,[10] magnesium,[1] manganese,[13] choline[14] and vitamin C[15] in addition to the more obvious relation of calcium, phosphorus, vitamin D and protein.

The effects of nutritional factors on the maintenance of bone, in contrast to their effects on development, have received little study. It has been assumed by some that osteoporosis, affecting large numbers of elderly women, may be related to faulty calcium intakes but expert opinion does not support this view.

FUNCTIONS OF CALCIUM OTHER THAN IN BONE FORMATION

The normal blood serum contains approximately 10 mg. of calcium per 100 cc., varying between 9 and 11 mg.,[19] while the red cells are essentially calcium free. Infants have a somewhat higher level which gradually decreases to the normal level with age.[6] The importance of this relatively small amount of calcium is apparent from the occurrence of tetany when the serum level is lowered. Although not well understood, the controlling mechanisms maintain a nearly constant blood level, in spite of large variations in intake and the great reserve in skeletal tissues. Approximately half of the serum calcium is bound as calcium proteinate and practically all of the remainder exists as ionized calcium. The calcium proteinate acts as a weak electrolyte and dissociation is governed by the mass law equation

$$\frac{(Ca)^{++} \times (Protein)^{--}}{Ca\ proteinate} = K,$$

or an approximation of it.[20] The regulation of

muscle irritability is dependent upon the serum Ca^{++}, but this is not a simple relationship. The amounts and ratios of Ca^{++}, Mg^{++}, Na^{+}, K^{+} and pH and probably other factors are involved.[6] Calcium is required also for normal nerve transmission.[9]

The clotting of blood requires prothrombin, Ca^{++}, and thromboplastin from injured tissues or platelets to form thrombin. Calcium has been shown to activate several enzymes including adenosine triphosphatase, succinic dehydrogenase, lipase, and some of the proteolytic enzymes. The permeability[3, 4] of membranes and perhaps of cells is influenced by calcium since the integrity of the intercellular cement substance apparently is dependent upon the calcium supply. Calcium also is an essential component, along with intrinsic factor, of the physiological mechanism for the absorption of vitamin B_1 from the intestinal tract and the adsorption of the vitamin on the cell membrane.

FACTORS AFFECTING CALCIUM ABSORPTION

Although there are considerable individual differences, human beings utilize calcium rather inefficiently. A growing rat may absorb practically 100 per cent of dietary calcium but only 20 to 30 per cent is usually absorbed by human beings. Many factors influence the actual amount absorbed.

Calcium Need.—It may be taken as practically a biological law that the body utilizes material more efficiently when in need. One may note the much better utilization of calcium in growing rats as compared to adult animals.[6] Similarly Ceylonese children with very low calcium intakes have more efficient utilization of dietary calcium than children studied in the United States.[27] Macy[28] showed that three boys fed a standard diet retained an average of 374 mg. of calcium per day during the experimental period. Another similar group which had received a high calcium diet for approximately two months prior to the study retained only 103 mg. of calcium per day.

Calcium Level in the Diet.—Raising the calcium intake may be expected to increase the absorption to some extent. In studies on preschool children[29] fed 339, 555, 704 and 904 mg. of calcium per day the retentions of calcium were found to be 62, 103, 125 and 154 mg. per day respectively.

Phosphates and Ca:P Ratio in the Diet.—It is generally taught[30] that a calcium phosphorus ratio of approximately 1:1 is ideal and that high concentrations of one ion precipitate the other as the insoluble calcium phosphate. Shohl and Wolbach[30a] clearly showed that in rats deprived of vitamin D the extent of rickets was a function of the calcium phosphorus ratio. The evidence in adult human beings is less convincing.[31–33] It appears likely that the importance of the calcium phosphorus ratio as a practical problem has been overemphasized.

Phytic Acid.—Much of the phosphorus in cereals occurs as phytic acid, the hexaphosphoric acid ester of inositol.[34, 35] Calcium phytate is relatively insoluble. Thus, the formation of calcium phytate in the gut should decrease the available supply of both phosphorus and calcium. Decreased absorption of calcium as an effect of phytate has been demonstrated in

several species including man.[36] Feeding diets very high in whole wheat may produce fecal losses greater than the calcium intake.[37] Many of the details concerning the utilization of phytic acid phosphorus and its effect on calcium absorption are still unclear.[36]

Iron, Strontium, Beryllium, Etc.[6]—Materials which form insoluble phosphates interfere with phosphorus absorption. This is not a complete explanation since strontium rickets does not respond to vitamin D.[38] It is of interest that Schorr[38a] has suggested that strontium may be beneficial as an adjunct to calcium in cases where calcification is abnormal.

Protein.—The addition of protein or amino acids to certain diets has been shown to increase calcium absorption.[39] Changes in the gastro-intestinal pH or formation of soluble calcium complexes with amino acids have been suggested as the explanation.

Fat.—Sprue, steatorrhea, biliary fistula, and other conditions in which fat is poorly absorbed interfere with calcium absorption,[40] probably by the formation of large amounts of insoluble calcium soaps.[36] On the other hand fats have been shown to have an antirachitic effect in rats.[36a] In normal individuals the effect of fat is probably minor.

Citric Acid.—Beneficial effects of citric acid and citrates in experimental rickets[6] have been observed and they have been used in the treatment of rickets and osteomalacia.[41] Presumably calcium absorption is increased. Recent studies have failed to show increased absorption of calcium in normal man,[4] however the citric acid content of bones and serum is low in rickets[43, 44] and is increased by vitamin D therapy. Nicolaysen and Nordbo[45] failed to find injected citrate effective in the cure of experimental rickets.

Oxalates.[36]—Oxalates form very insoluble salts and render calcium unavailable. A few vegetables such as rhubarb and spinach contain oxalic acid in excess of their calcium content. While such foods certainly can not be recommended as calcium sources, neither should undue importance be given to the oxalic acid they contain.

Intestinal Acidity.—A lower intestinal pH favors calcium absorption. A partial explanation of the poor utilization of calcium in rickets may be related to a high intestinal pH. Improved calcium absorption from feeding lactose may be due to lactic acid fermentation with increased acidity in the gut.[2] Hydrochloric acid in the stomach is of importance for similar reasons.[41, 46] The relationship between achylia gastrica and osteoporosis has been demonstrated experimentally in dogs.[47]

CALCIUM EXCRETION

Fecal Excretion.—Some calcium appearing in the feces comes from the body rather than from the diet, as has been directly demonstrated by the injection of radio calcium. It appears likely that there is no regulated excretion[36] in the usual sense but rather that the calcium secreted into the intestine becomes intimately mixed with that supplied in the diet and its absorption is affected by the same factors as affect dietary calcium.

Urinary Excretion.—Albright[41] places the kidney threshold for calcium at approximately 7.0 mg. of calcium per 100 cc. There is considerable evidence that the threshold is not the primary factor governing excretion

Children and young animals fed very low calcium diets excrete very little in the urine[26] although normal blood levels are maintained The hormone of the parathyroid is believed to be involved in regulating kidney excretion but understanding of the mechanism is incomplete

The level of calcium in the urine appears to be in large part dependent upon endogenous factors[36] characteristic of the individual other factors being equal Increases in calcium absorption for example will raise the level of excretion but the baseline of excretion remains different in different individuals Age and sex are not important variables if excretion is expressed on a unit weight basis[51]

CALCIUM REQUIREMENTS

Determination —Two methods have been used to estimate calcium requirements For growing animals and children the total body content at different ages has been estimated from limited total body analyses and by various suppositions regarding the relationship between body weight and skeletal weight From such data it is possible to estimate the needs required to meet the daily deposition at different ages If the average retention of dietary calcium is known or can be estimated usually around 20 to 30 per cent of the intake the daily dietary need can be calculated T other method and the only one which has been used in studying adu requirements is the balance method This consists of measuring the tot intake of calcium and the total excretion in the feces and urine If the in take and output are equal the body is said to be in balance and is maintaining its *status quo* A positive balance (calcium retention) is shown by an excretion less than the intake and a negative balance by the reverse The calcium balance method has also been used with growing children and animals In the growing animal a positive balance is the normal situation of course if the bones are not to be depleted The same must be true in pregnancy and lactation In the normal adult only balance is required since the body is not increasing in size The limitations of the balance method have not been generally realized

Infants and Children —Holmes[6] has reviewed the various methods employed to estimate dietary needs during growth There is insufficient data for clear-cut preference among these methods but the assessment of Mitchell and Curzon[5] is based upon the daily weight gains They assume the fresh skeletal weight to be a constant percentage of body weight the calcium content of the infant at birth to be 0.8 per cent and in the adult man 1.5 per cent and that the calcium content of the body increases regularly so as to yield the final value of 1.5 per cent at adulthood This final value of 1.5 per cent was arrived at by comparisons with other adult animals and the limited number of analyses on adult human bodies[26] The net calcium retentions to meet the growth curve are shown in Figure 11 The high requirements during the first year and during the pubertal growth spurt are clear

The normal infant according to this curve would need to store approximately 450 mg of calcium per day during the first month but only 123 mg per day at the end of the first year If one assumed that a 35 per cent

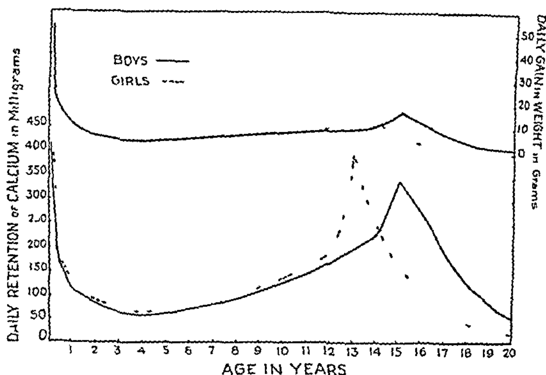


Fig. 11 —Estimated daily rates of calcium deposition in children as calculated by Mitchell and Curzon [64]

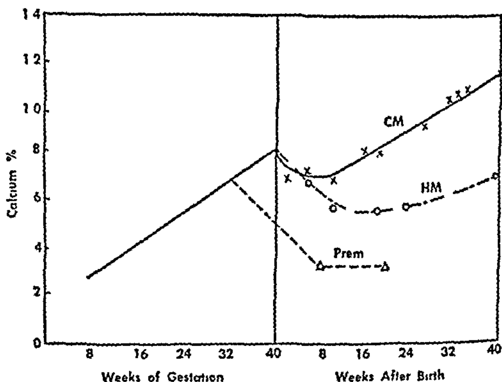


Fig 12 —Changes in calcium concentration in the fetus and infant CM infants fed cow's milk, HM infants fed human milk, Prem premature infants fed human milk. (Stearns courtesy of Physiological Review)

retention of dietary calcium might occur at this time A liter of cow's milk or 4 liters of mother's milk would be required to meet the demands during the first month Obviously the infant especially when breast fed will fail to obtain this amount of calcium Stearns[53] has determined (Fig 12) the rates of calcium deposition in normal infants Calcium deposition does not keep pace with the rate of body growth during the first months of life particularly in breast feeding Nitrogen retention and muscle development are similarly less rapid in the breast fed infant as compared to the artificially fed infant The significance of these changes is not readily apparent since most nutritionists are unwilling to believe that cow's milk is superior to human milk for the human infant and the breast fed infant is not known to suffer any nutritional disadvantage compared to those artificially fed Maximum development may not necessarily be optimum

On the other hand studies on calcium retention in children generally have shown larger retentions than those estimated to be necessary by Mitchell and Curzon These have been summarized by Holmes[26] Whereas retentions of 100 to 200 mg per day theoretically meet the need of children from two to ten years of age the experimental values found are often as high as 300 to 500 mg per day This is presumptive evidence that under usual circumstances the rate of calcium deposition does not correspond closely to the rate of body growth It seems likely that calcium is stored to a certain extent during the period when growth is not rapid and that this may serve as a safeguard for those periods when growth is rapid and the calcium intake less adequate

The pubertal growth spurt greatly raises the calcium need Since the utilization of calcium during this period appears to be approximately 20 to 25 per cent of the dietary calcium, a retention of 300 to 400 mg per day would require an intake of about 1 2 to 1 6 grams per day While such critical periods may be covered partially by relatively large retentions at an earlier age the need for high milk intakes or other calcium sources is apparent The need is related to the growth spurt and not to chronological age At this period of great need the dietary habits especially of girls are apt to be quite unsatisfactory

Adults —Contrary to the situation in children where calcium retention is clearly desirable the well nourished adult has no apparent need for more calcium than that required to maintain the body stores * The preferred method of evaluating calcium balance data is shown in Figure 13 A spot diagram is prepared showing the intake and output of each individual studied The mean regression line through the data is calculated, giving the average output at various intakes Individuals in balance will fall upon the line labelled calcium equilibrium The points above the line represent positive balance and those below the line represent negative

* Studies reviewed by W M Cobb (*Problems of Aging* edited by A I Lansing Williams & Wilkins Co Baltimore 1952) suggest that there may be a gradual increase in skeletal weight up to age thirty five a variable decrease until age sixty five and more rapid losses thereafter The skeletons upon which this kind of data have been collected have not been of known nutritional history and the significance of these changes if they occur generally is not known It is impossible at this time to evaluate the data in terms of health desirability or non-desirability cause and effect

balance The mean intake required to maintain balance in the population summarized by Mitchell and Curzon is at the intersection of the two lines, or approximately 10 mg per kg of body weight per day A 70 kg man would thus require about 0 7 gm of calcium to maintain balance However, since there is considerable variation about the line, a considerable number of individuals would be in negative balance at intakes of 10 mg per kg per day Essentially all would be in balance or retaining calcium at 1 0 gm per day

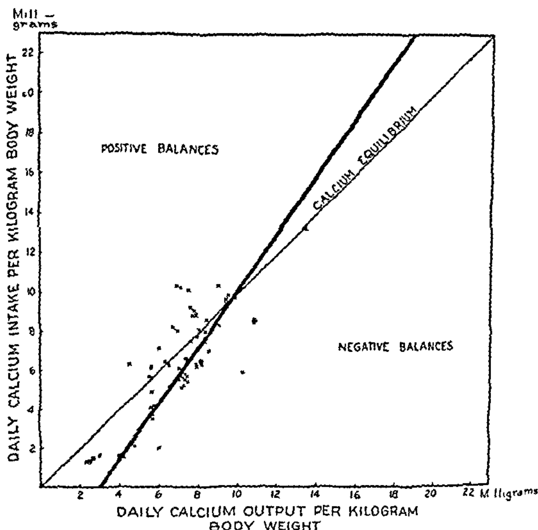


FIG 13 —Calcium output at various calcium intakes in 139 experiments upon adult subjects (Mitchell and Curzon, *Actualities Scientifique et Industrielles*, Herman & Co)

The foregoing discussion represents the reasoning upon which recommended allowances for calcium have been based [54] This interpretation may be questioned It must necessarily be true that the average adult of any stable population must be in calcium balance very elderly people excepted If this were not so, one would find the adults either wasting away and eventually dying with very depleted calcium stores or eventually ending up with great excesses of body calcium Neither is true Thus, practically any normal adult person must be assumed to be in balance in the long run The same reasoning must apply to most of the world's

population existing upon diets quite low in calcium. Average intakes in countries where milk is not a common food and where there are no other unusual sources of calcium is approximately 300 to 400 mg per day, yet the adults must maintain balance. Studies in Peru,[43] India[55] and other areas have demonstrated this to be true. Adults accustomed to low calcium diets are found on the average to be in balance at the level of intake supplied by their usual diet. Hence the author has concluded[56] that the determination of the level of calcium required to maintain balance in an adult simply estimates the previous intake of calcium in the individual.

If this is true, it is of particular importance to study those individuals who are accustomed to low calcium diets to see whether they can be shown to suffer any ill effects from this cause. Unfortunately studies on such groups are very limited. It can be said that as far as is known clinical calcium deficiency is not common in these groups.

The experiments of Sherman and co-workers[57–59] showed that rats fed from weaning or through several generations were benefitted by levels of calcium intake above those usually considered adequate. Length of life and reproductive performance were the measures of improvement. This is presumptive evidence that high levels of calcium may be of some importance in human nutrition but it has been pointed out that human beings do not eat the same diet at all periods of life and the effects of a calcium deficiency in studies such as these would most likely occur during growth or in pregnancy and lactation. The experiments thus do not necessarily demonstrate high calcium needs in adult life.

The adaptation shown by peoples eating low calcium diets is achieved by a more efficient absorption of dietary calcium than in persons accustomed to higher intakes.[48, 60] The adaptation of a person accustomed to high calcium diets when placed upon low calcium diets has never been adequately studied. It must consist of a period of negative calcium balance during which the excretion gradually falls until eventually balance is again achieved. The limited data available indicate that this must be a very slow process in many individuals, much more rapid in others.[36] The effects of this adjustment upon the health of the individual, the amount of calcium lost from the body, whether this is eventually regained and other similar questions remain to be studied.*

* Henry and Kon (*Brit. J. Nutr.* 7, 147, 1953) compared rats fed relatively high and relatively low calcium diets throughout the growth period and in adulthood. On the low calcium diet used the rats grew slightly less rapidly than those upon the high calcium diet. However, when adulthood was reached the total body calcium was essentially the same in the two groups of animals. The animals adapted to the low calcium diet retained calcium much more efficiently even in old age than those fed larger amounts. The authors speculate that the bone salts may be laid down in a more stable form. Studies upon dogs (Gershoff, Legg and Hegsted, *J. Nutr.* 64, 303, 1958) fed different levels of calcium revealed similar results. Boda and Cole (*J. Dairy Sci.* 37, 360 [1954]; Ibid. *39*, 66 [1956]) concluded that protection from tetany following parturition in dairy cattle was achieved by feeding them a low calcium diet prior to parturition. It is suggested that the feeding of a relatively low calcium diet stimulates the parathyroids (or other mechanisms involved in calcium mobilization) and the animal is thus better able to respond to the great calcium need during lactation. Thus there is some experimental evidence that adaptation to relatively low calcium diets may be beneficial (Hegsted, Nutr. Rev. *15*, 257 [1957]).

It must be concluded that our knowledge of calcium requirements is much less satisfactory than has been assumed Numerous questions remain to be answered Although the possibility that the formation of kidney stones and calcification of soft tissues may be influenced by high calcium intakes must be borne in mind, there is no evidence that high calcium intakes is a primary factor Since clinical signs of calcium deficiency are practically nonexistent in the United States insofar as is known, in spite of large variations in calcium intake we may express some doubt that calcium deficiency is either as prevalent as many have stated or as pressing a nutritional problem in the world as has been assumed Better methods of appraising calcium needs and detecting calcium deficiency are urgently needed The recommended allowance[54] of 0 8 gram of calcium per day for adults would appear to be adequate As indicated by the summary of Mitchell and Curzon,[5] the average adult studied in the United States should maintain balance at 0 7 to 0 8 gm of calcium per day

Pregnancy and Lactation —The requirements for calcium obviously are increased when bone is being formed The requirements during pregnancy are considered to be those of the adult woman plus the amount required by the fetus It has been estimated[57] that the fetus requires 25, 50, 84, 125, 175, 234 and 300 mg daily, respectively, for the last seven lunar months To estimate the increased dietary need, these values must be increased by a factor accounting for the efficiency of absorption If one assumes a maximum utilization of 40 per cent of the dietary calcium, 750 mg of calcium would have to be supplied to meet the requirement of 300 mg for the fetus during the last month This amount added to the estimated need of the normal woman would give something over 1 5 gm of calcium per day

The calcium requirement of the lactating woman depends to a considerable extent upon the volume of milk produced Each 100 cc of normal human milk contains approximately 30 mg of calcium Assuming a 40 per cent utilization of dietary calcium, 75 mg of calcium in the diet would be required to cover this additional need The volume of milk produced varies greatly with individuals, time of lactation, etc , but may be expected to average about a liter per day This represents an additional requirement above the maintenance amount of about 750 mg per day

The recommended allowances for the pregnant and lactating woman[54] are 1 5 and 2 0 gm of calcium per day These amounts should easily prevent any drain upon the skeletal tissues except under unusual circumstances Obviously, many women do not consume diets containing these amounts of calcium Approximately a liter of milk per day in addition to the other foods in the diet would be needed to give a diet containing 1 5 gm of calcium and proportionately more to give 2 0 gm It should be noted that the philosophy behind such estimates is that a temporary depletion of the body is undesirable On the other hand, it is fairly well accepted that the high producing dairy cow is often incapable of absorbing sufficient calcium from the diet, regardless of dietary level, to meet such large needs Depletion thus occurs during high production and calcium is stored as milk secretion lessens or ceases Neither the disadvantages nor advantages of this in terms of health and long time performance of the cow

or of humans has been shown In any event, it is clear that the body has reasonably good defenses against temporary periods of calcium lack

That calcium requirements are indeed high during this period is clear from the occurrence of osteomalacia in pregnant and lactating women in countries such as China[61] where the diet is generally very low in calcium Interestingly enough, these cases respond to vitamin D therapy even though the dietary intake of calcium is not markedly increased Calcium therapy alone is not satisfactory The difficulty of distinguishing between lack of calcium and vitamin D is apparent

Old Age —Increasing interest in geriatrics and the relatively high incidence of fractures and osteoporosis in elderly people has aroused considerable interest in the calcium requirements in old age While any possible influence of nutrition deserves serious consideration osteoporosis is now generally considered to be due to faulty metabolism of the protein rich bone matrix, and calcium metabolism is not primarily involved[41] Starvation with low protein intakes results in 'hunger osteoporosis Faulty protein metabolism is the cause of the disease in the postmenopausal period and in Cushing's syndrome Immobilization diminishes the activity of the osteoblasts and "osteoporosis of disuse may result[6]

Elderly people and old animals tend to lose body calcium[63,64] Feeding high levels of calcium will temporarily prevent this loss This has been interpreted as showing that calcium requirements are high in old age No long time studies have been reported nor is there convincing evidence that high intakes during the adult period are beneficial in preventing the development of osteoporosis In view of the many unknowns however a conservative attitude suggests that calcium intakes should be relatively high The possible effects of other nutrients deserves more study

Excessive Calcium Intake —A number of clinical conditions are associated with evidence of excessive calcium in the serum and urine or calcification of the soft tissues These would include such various conditions as the idiopathic hypercalcemia of infancy the milk alkali syndrome, hypercalcuria, and kidney stones These conditions are more appropriately discussed elsewhere (*See* Chapter 25) There is probably no adequate evidence to implicate high calcium intakes as the principal causative factor in any of these conditions but it is logical that high intakes may often contribute since low calcium intakes are an integral part of effective therapy

HORMONAL INFLUENCES

Parathyroid Hormone[65]—The intimate relation between this hormone and calcium metabolism is well known The administration of the hormone results in an increase in the serum phosphorus and calcium and increased excretion of the two elements in the urine Albright[41] considers the effect on calcium metabolism to be secondary to an increased excretion of phosphate by the kidney The loss of phosphate causes a necessary withdrawal of phosphate from the bones and the calcium is released simultaneously The opposing view is that the primary action of the hormone is on the bone influencing the activities of the osteoblasts and osteoclasts high levels resulting in resorption of bone Some authors believe that either

mechanism is an oversimplification Milne[66] concluded that in the hyperparathyroid state the chief action was the renal effect whereas in the normal subject the main action was upon the bone

This hormone does not appear to influence absorption of calcium[36, 41] although the low serum calcium in hypoparathyroidism may be at least partially alleviated by calcium administration

Thyroid —In hyperthyroidism high excretions of calcium and phosphorus are found and osteoporosis is described as the result of this disease Although it has been suggested that the thyroid hormone has a direct action upon the calcium threshold of the kidney, Albright[41] believes that these effects are secondary to a negative nitrogen balance and insufficient bone matrix

Steroid Hormones —As has already been mentioned several times, bone growth must be related to calcium retention and the dissolution of bone to calcium losses, regardless of the cause of these changes The beneficial effects of the sex hormones in senile and postmenopausal osteoporosis and the improved calcium and phosphorus balances thus obtained are generally interpreted as an influence upon protein metabolism and bone matrix formation [41]

The effects of sex hormones upon the skeletal tissues of various species has been reviewed by Gardner and Pfeiffer [67] In birds, egg laying is associated with marked changes in serum calcium and the mobilization of large amounts of calcium These authors conclude that estrogens may stimulate osteoblastic action and that large amounts of the steroid sex hormones may inhibit cartilage growth and therefore bone growth Small amounts especially of androgens, may stimulate bone growth

PHOSPHORUS

Phosphorus is not often of concern to the nutritionist since the diets of human beings are generally quite adequate in phosphorus On the other hand, phosphorus deficiency is not uncommon in cattle and other species in which forage is the principal food Grasses and hays usually contain more calcium than phosphorus and this is particularly true in areas where soils are low in available phosphorus In such areas "aphosphorosis" occurs [68] The deficiency disease is characterized by a perverted appetite and chewing of bones, wood dirt, etc , is typical As the disease progresses the animals lose their appetite, the general appearance becomes poor, the joints stiff, and the bones become fragile and easily broken No similar disease in man is known, although undoubtedly it could be produced by feeding low phosphorus diets

Any complete discussion of phosphorus metabolism would require practically a complete consideration of the metabolic processes in the body Phosphorus compounds play a central role in the transformations of energy in the body and an understanding of the role of "high energy phosphate bonds" has been one of the major recent achievements in biochemistry Adenosine triphosphate and the nucleotides formed from several of the vitamins are essential in the catabolism and anabolism of carbohydrates, fats and proteins The phosphorus-containing nucleoproteins make up a

large portion of the nuclear material and also occur in the cytoplasm of all cells and are key materials in the processes of cell division, reproduction and the transmission of hereditary characteristics. The viruses which somehow modify normal cell function to reproduce themselves are also nucleoproteins. Among the fat soluble materials one finds a great variety of phospholipids. Numerous advances in the identification of these substances has been made in recent years.

The blood and serum phosphorus is generally classified as lipid, ester and inorganic phosphorus. The inorganic phosphorus of the serum in infants is between 5 and 6.6 mg./100 cc. and gradually diminishes during childhood to the adult level of 3 to 4 mg./100 cc. Ordinarily there is a reverse relationship between the serum inorganic phosphate and the serum calcium but not always so.

Phosphorus Absorption and Excretion.[41]—*It is likely that most if not all of the phosphorus is absorbed as free phosphorus.* The various phosphate esters must thus be hydrolyzed probably by the various phosphatases, prior to absorption. The absorption of inorganic phosphorus is intimately related to the amount of calcium in the diet or other similar materials which may form insoluble salts and thus related to the absorption of calcium as well.

Fecal phosphorus represents both unabsorbed phosphorus and phosphorus secreted into the tract. The amounts from the two sources are not well defined and the absorption of both is presumably affected by the same factors. Under ordinary conditions the feces contain about 30 per cent of the amount in the diet. Dietary phosphorus is thus absorbed better than calcium and consequently the kidney excretion of phosphorus is much greater than that of calcium.

Urinary phosphorus is largely inorganic phosphate, the amount depending primarily upon the amount absorbed from the intestinal tract. Since the oxidation of sugar requires phosphorus there is a temporary lowering of serum phosphates and of phosphate excretion after the ingestion of carbohydrates.[69] Catabolism of body tissues in starvation, acidosis, etc. releases considerable phosphorus which is excreted by the kidney. There has been considerable discussion and disagreement as to the role of vitamin D both in the absorption and kidney excretion of phosphorus. The reader is referred to the section on vitamin D, page 310.

Phosphorus Requirements.—*Relatively little data are available upon actual phosphorus requirements under different conditions.* The balance studies of Sherman[9] indicated a need for approximately 0.88 grams per day to maintain balance in the normal adult. The limitations of balance studies referred to in the section upon calcium requirements apply in this case and it may be suspected that the usual intake of the subjects studied was estimated. The Food and Nutrition Board concludes that "Available evidence indicates that phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation. In the case of other adults the allowances should be approximately 1.5 times those for calcium. In general it is safe to assume that if the calcium and protein needs are met through common foods, the phosphorus requirements also will be covered because

the common foods richest in calcium and protein are also the best sources of phosphorus "

Calcium and Phosphorus Content of Foods —In Table 18 are presented some average values for the calcium and phosphorus content of various kinds of foods These foods have been selected from a more extensive food table[71] simply to indicate the relative levels in the different classes of foods, meats, legumes, cereals, etc It will be noted that most common foods other than milk and the green leafy vegetables contain considerably more phosphorus than calcium, thus accounting for the greater interest in calcium in human nutrition It should be borne in mind, in the evaluation of a food as a potential or actual source of nutrients, that the total intake must be considered as well as the amount of nutrient per unit weight Those materials eaten in large amounts are often more important sources of a particular nutrient than those which contain large amounts

TABLE 18 —AVERAGE CALCIUM AND PHOSPHORUS CONTENT OF SELECTED FOODS

Food	*Calcium* *mg /100 gm*	*Phosphorus* *mg /100 gm*
Cow s milk	118	93
Human milk	32	13
Beef	11	170
Pork	7	117
Beans, dry	163	437
Peas, dry mature	57	388
Potatoes	11	56
Sweet potatoes	30	49
Carrots	39	37
White bread (4% nonfat milk solids)	79	92
White bread (no milk solids)	13	77
Corn meal	6	99
Oat meal	55	105
Cabbage	46	31
Kale	225	62
Lettuce	22	25
Apples	6	10
Grapefruit	22	18
Peaches	8	22
Brazil nuts	186	693
Peanuts	74	393

MAGNESIUM

There is considerable magnesium in the body, approximately 25 grams, and evidence that it is an essential nutrient for rats was obtained as early as 1926[72] McCollum and his co-workers[73] and others[74] have studied experimental magnesium deficiency in considerable detail Numerous enzyme systems require magnesium for their activity and considerable is known of its pharmacological action In spite of the rather extensive biological literature upon this element, practically nothing is known of its role in the health and disease of human beings This can be ascribed in part to inadequacies of the methods available for its determination Re-

newed interest and improved methods[75] are hopeful evidence that this period is passing

Magnesium Deficiency

Young rats fed a very low magnesium diet develop a classical syndrome in a few days There is a marked vasodilation seen primarily upon the ears, tail and feet This is followed by pallor and cyanosis which may lead to necrotic changes The animals become hyperirritable and may develop seizures and die Animals which do not die with convulsions may survive for a considerable period Pathologic changes in many tissues have been described Of particular interest is the calcification of many soft tissues and the deposition of calcium casts in the convoluted and collecting tubules of the kidneys It has been concluded that a primary result of magnesium *deficiency is a disorder in calcium metabolism*[76] *The magnesium require-*ment and the pathologic changes are dependent in part upon the calcium intake It has been noted that the pathogenesis is not unlike that of the "milk alkali syndrome" in man[77] and magnesium deficiency has been noted in calves fed exclusively upon milk diets[78]

Magnesium deficiency in cattle is seen in the disease called grass tetany" or grass staggers " This is characterized by hypomagnesemia, hyperirritability, tetany and convulsions[79] The epidemiologic studies indicate that it occurs in the spring when animals are turned out to lush pastures high in protein A high ammonia content in the rumen may interfere with magnesium absorption The disease has been produced by the addition of ammonium carbonate to the diet[80] It is probable also that the disease reflects an inability of some animals to mobilize magnesium from the bone[81]

Magnesium deficiency has been produced experimentally in several species Of particular interest is the finding that guinea pigs seem to require exceptionally large amounts for normal growth[82]

Magnesium Metabolism in Man

Magnesium is primarily an intracellular ion and adult fat free tissue contains approximately 43 mg per kilogram The serum level is approximately 2 meq/liter There is no satisfactory evidence of the normal requirement although it has been estimated that 250 mg a day is adequate for adults, this value being based upon balance studies[83] Values of 150 mg for infants and 400 mg during pregnancy and lactation have been suggested as adequate[84]

Decreased serum magnesium levels have been reported in various conditions including idiopathic epilepsy[85] eclampsia,[85] chronic nephritis,[86] acute pancreatitis,[87] delirium tremens, and alcoholic cirrhosis[88] The importance of these observations and whether or not they are characteristic remains to be demonstrated A normocalcemic hypomagnesemic tetany in a child, which responded to magnesium sulfate administration, has been reported and may represent a case of magnesium deficiency[89]

Magnesium sulfate has been used empirically as a sedative in the treatment of delirium tremens In more recent studies[90] it has been suggested

on the basis of serum levels and therapy, that a magnesium deficiency occurs Data are as yet insufficient for rigorous proof In all likelihood, if magnesium deficiency is important, some factor other than simple dietary lack is in volved, as has been observed in cattle with hypomagnesemia

Magnesium salts have also been used empirically in the treatment of coronary patients[91] This approach has received some experimental im petus by the observation[9] that hypercholesterolemia in animals increases the magnesium requirement, and that high levels of dietary magnesium decrease the degree of experimental atherosclerosis It has also been reported[93] that the serum magnesium levels in Bantu Negroes, known to be relatively immune to atherosclerotic heart disease, are higher than the serum levels in a white population of the same age with extensive atherosclerosis Confirmation, particularly with improved analytic methods, is needed

Low serum magnesium levels have been observed[94] in patients main tained postoperatively upon magnesium-free fluids parenterally and nasogastric suction Evidence of magnesium deficiency, as indicated by various signs of neuromuscular irritability, has been observed, as well as the response of some patients to magnesium treatment

The relatively large amounts of magnesium in the body, its known bio chemical functions, and the limited studies available, are indicative of the need for much more extensive study both from the clinical and the nutri tional point of view

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Chapter 10

A Iron and the Essential Trace Elements

By Carl V Moore

Interest in the nutritional importance of trace elements has been reawakened by the increasing list of enzyme systems in which trace elements have been identified, and by the recognition of additional manifestations of trace element deficiency. Eight of the elements found in animal tissues in minute amounts are known to be essential: cobalt, copper, fluorine, iodine, manganese, molybdenum, selenium, and zinc. Iron is needed in larger quantities and cannot properly be classified as a trace substance. However, since its function in hemoglobin and red blood cell physiology is so closely allied with copper and cobalt, there are physiologic reasons for including it in this chapter. Many other elements—aluminum, arsenic, barium, boron, bromine, caesium, chromium, lead, lithium, nickel, rubidium, silicon, silver, strontium, tellurium, tin, titanium, and vanadium—are also frequently found in traces in animal tissues.[1] There is no convincing evidence, however, that they are necessary to life; they may merely be accumulated in tissues because they are present in food, and the body finds it difficult to excrete them. Some of these minerals may be shown to be indispensable when methods of study become less crude, but at present they are of medical interest largely because they may accumulate in toxic amounts. Discussion, therefore, will be limited to iron, copper, cobalt, molybdenum, fluorine, iodine, manganese, selenium, and zinc.

Proof that any element is essential to life depends largely on the demonstration that when it is deficient, certain signs or metabolic defects result and that abnormalities can be corrected by replacement therapy. Experiments on animals have provided these data for copper, manganese, and zinc. Some phases of trace element nutrition cannot be placed on a simple quantitative basis; the chemical form in which the element is made available to the body may be critical. For instance, cobalt is an integral part of the vitamin B_{12} molecule; ruminants raised on cobalt-deficient pastures develop a disease which responds to the administration of vitamin B_{12}. Cobalt alone is without therapeutic value in these animals unless it is given by mouth so that it can be synthesized into vitamin B_{12} by the bacteria in the forestomach. Furthermore, dietary interrelationships of trace elements, as between copper and molybdenum, also influence nutritional requirements. Molybdenum is a part of the xanthine oxidase molecule, and an organic selenium compound (Factor 3) protects against the development of dietary liver necrosis in the rat. Inadequacies of fluorine have been shown to increase the incidence of dental caries.

Most of the information about essential trace elements has been derived from experiments on animals and many of the data have not yet been related to disease in the human. An attempt will be made, however, to *emphasize those observations which seem to have the most definite clinical* implications.

IRON

Iron is a component of hemoglobin, myoglobin, the cytochromes, *catalase, peroxidase, and certain other enzyme systems. As a part of* these heme complexes and metalloenzymes, it serves important functions in oxygen transport and cellular respiration. The body of a normal adult contains approximately 2.5 to 5.5 grams of iron, depending largely on the body weight and the circulating mass of hemoglobin. About 50 to 60 per cent of this total *is found in hemoglobin and 10 to 20 per cent in myo-*globin; the important cellular enzyme portion is quantitatively small; the remainder is stored chiefly in organs rich in reticulo-endothelial cells (liver, spleen, bone marrow). Deficiency of iron leads to the development of hypochromic microcytic anemia—probably the commonest of all deficiency diseases, and certainly one of the two or three most common anemias in the world today. Iron excess or overload is of increasing clinical importance; it occurs in hemochromatosis, transfusion hemosiderosis, or as a consequence of prolonged, excessive oral iron intake (*i.e.*, cytosiderosis among the Bantus in Africa).

Metabolism.—Information accumulated during the past decade makes it possible to define the main metabolic pathways of iron in terms that are at least *semiquantitative (Fig. 14). As a result, a much clearer under-*standing of the factors involved in the pathogenesis of iron deficiency and of *iron overload is now possible. Our knowledge of the enzymatic iron* in cells, and of the biochemical processes which control the absorption, storage, mobilization and utilization of iron is still meager.

1. *Absorption.*—The average adult diet in the United States provides about 12 to 15 mg. of food iron; for people who eat large amounts of meat, the value may be 20 mg. or more. The mechanisms determining the amount of iron absorbed and responsible for transfer of the metal across *mucosal cell membranes are unknown, but the following statements seem* reasonably well established.

(*a*) Ingested iron must be reduced to the ferrous form in the stomach and small intestine before it can be absorbed.[2,3]

(*b*) Absorption is probably greatest in the upper portion of the small intestine and decreases progressively in the more distal segments of the intestinal tract.[4] The reason for this diminishing gradient has never been adequately explained. *The ileum may possibly be as efficient as the duo*denum in absorbing iron but may have less opportunity because insoluble complex combinations of iron are probably formed by the time the digestion mixture reaches distal portions of the small intestine. Resorption from the stomach has also been demonstrated, but the amount is probably not large.

(*c*) Patients with iron deficiency and with increased rates of red blood *cell formation absorb iron more efficiently* than do normal persons.[5-7]

(*d*) The normal adult human absorbs an average of 5 to 10 per cent of iron from foods common in the American diet and from bread fortified with iron in the food fortification program [5 8–14] With a dietary intake providing 12 to 15 mg of iron per day the retention therefore, would be approximately 0 6 to 1 5 mg Infants and children under the age of 3 years adsorb somewhat more than 10 per cent [11] while iron deficient children and adults may absorb as much as 20 per cent or more [5 8 13 14] Relatively large doses of ascorbic acid or other reducing substances increase absorption in part at least by promoting the reduction of the ferric iron in food to the ferrous form [5 13] These results have been obtained with balance

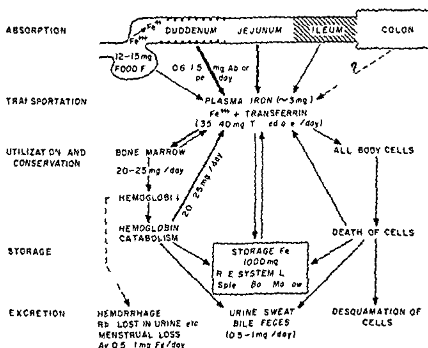


Fig 14 —Iron and the Essential Trace Elements

studies [9] by feeding foods tagged with radioactive iron,[5 8 11–14] or by adding tracer doses of inorganic radioiron to normal meals [10 13] A representative series of experiments with tagged foods is illustrated in Figure 15 The iron in hemoglobin is assimilated as well as from most foods [7]

Gastric acidity seems to be less important in promoting iron absorption than was formerly thought If food is mixed with enough 1N HCl to reduce the pH to 1 5 and then given to a patient with achlorhydria absorption is not enhanced With increasing bulk or phytic acid content of the diet the absorption of iron tends to decrease [10] Assimilation is poor in patients with steatorrhea [7] After partial gastrectomy absorption of tracer doses of inorganic iron given under fasting conditions may remain normal

but is adversely affected by a full meal Furthermore, such subjects fail to increase their absorption significantly when they become iron deficient[11]

(e) Some unknown mechanism causes mucosal cells to assimilate iron with greater efficiency when the body is iron deficient or erythropoiesis is stimulated, and to reduce absorption when iron stores are heavy Granick has demonstrated that when iron enters the mucosal cell it combines with a protein apoferritin, to form ferritin, a compound in which colloidal iron hydroxide—iron phosphate micelles are bound to apoferritin in amounts up to 23 per cent by weight[16] He postulated (1) that apoferritin is constantly being formed and broken down, its degradation stopping when ferritin

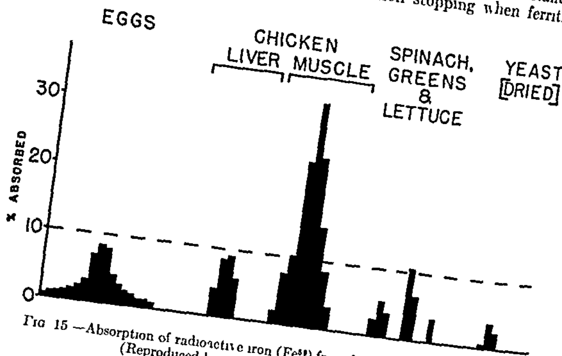


FIG 15 —Absorption of radioactive iron (Fe^{59}) from foods by normal persons (Reproduced by permission of the J A M A)

is formed and (2) that once the mucosal cells are saturated with ferritin molecules absorption stops by virtue of a "mucosal block" until the ferritin gives up its iron to the blood stream It was natural to think that anemia and a low serum iron might hasten the transfer of ferritin iron to capillary blood and thus prepare the way for further absorption but the hemoblobin and serum iron levels have been shown not to be determining factors[6,17,18] In addition, recent evidence indicates that while ferritin may be the mediator of iron absorption, its concentration within mucosal cells does not determine how much iron will be taken up Absorption continues even after maximal concentrations of ferritin are reached in the mucosal cells of the intestine and may decrease at a time when the mucosal concentration of ferritin is actually decreasing[19,20] The whole concept of a mucosal block should be abandoned[18] and a fresh new search made for the biochemical factors which control iron absorption

2 *Transportation* —Iron is absorbed directly into the blood stream rather than through the lymphatic channels In the plasma, it is oxidized to the ferric state and combined with a specific iron binding protein,

a beta-1 globulin which has been called transferrin, siderophilin or simply the iron-binding protein[21] Each molecule of this specific plasma protein can combine with two atoms of iron, there is enough of it in plasma to bind from 300 to about 450 micrograms of iron per 100 ml (iron binding capacity) The amount of iron in plasma, however, varies normally from about 50 to 180 micrograms per 100 ml, only a portion of the transferrin therefore is bound

The iron in plasma is transport iron, the hub of iron metabolism (Fig 14) In an individual with a total plasma volume of 3 liters and a normal plasma iron level there are only about 3 or 4 mg of transport iron in the total circulating blood volume at any one time The turnover rate, however, is rapid, averaging about 0 56 mg per kilogram of body weight

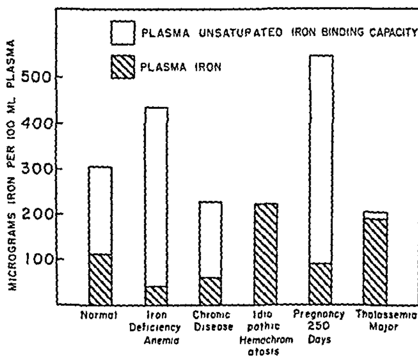


Fig 16 —Serum iron and iron binding capacity relationships in normal subjects and in patients with various disturbances of iron metabolism

per day[20, 3] This quantity in a man who weighs 70 kilograms would be roughly 35 to 40 mg per day A relatively large percentage of it goes to the bone marrow where it is used for hemoglobin synthesis, but since only 20 to 25 mg are needed per day for new hemoglobin the unused portion is presumably largely returned to plasma From plasma the iron may also go to organs of storage to tissues other than bone marrow for the formation of myoglobin and cellular enzymes or to sites of excretion

When iron deficiency develops the iron binding capacity rises to levels of 450 micrograms per 100 ml or greater, and the plasma iron falls to less than 50 micrograms per 100 ml With anemias of infection both the plasma iron and the iron binding capacity are low In hemochromatosis, the

plasma iron characteristically becomes elevated enough to saturate the iron binding protein The iron binding capacity increases as much as 50 per cent during the last half of pregnancy and returns slowly to normal during the two months following delivery Changes in these two values associated with a variety of diseases have proved valuable in differential diagnosis and in studies of disease pathogenesis (Fig 16)

Recent experiments by Jandl have demonstrated that iron is transferred from transferrin to young red cells more efficiently than when it is in simple solution [24] When tissues pick up the iron, however, the transferrin remains in plasma [21, 4]

3 *Storage and Tissue Iron* —The work of several investigators has demonstrated (*a*) that the amount of iron stored in the tissues of a healthy adult is approximately 1 gram, (*b*) that the liver and spleen constitute the chief storage sites and (*c*) that storage iron is found intracellularly in a protein complex as ferritin, and as hemosiderin [25] With chemical and electron microscopic studies, hemosiderin has been shown to be a condensation or clustering of ferritin molecules [26] In the liver and spleen of normal animals, there is a slight preponderance of ferritin over hemosiderin iron [27] With increasing concentrations of tissue iron, this ratio is reversed, and at high levels the additional storage iron is deposited as hemosiderin Of great physiologic importance is the fact that both forms are capable of being mobilized for hemoglobin synthesis when the need for iron exists The mechanism by which ferritin iron is released to the plasma seems to involve a reduction by xanthine oxidase [8]

Increased iron stores may be brought about in two ways

(*a*) Without actual increase in total body iron When an anemia develops because of hemolysis or aplasia of the marrow, there is less iron in circulating hemoglobin, more in tissue stores

(*b*) A true increase in total body iron is found in patients with hemochromatosis, transfusion hemosiderosis after excessive and prolonged iron therapy, and in cytosiderosis The amount in tissues may exceed 30 gm, depending on the cause and duration of the metabolic defect

A rough estimation as to whether iron stores are deficient or excessive may be made from the serum iron, total iron-binding capacity, and stainable iron in bone marrow aspirates [9]

	Serum Fe	*Total Iron-Binding Capacity*	*Stainable Iron in Marrow*
Normal	50–180 γ/100 ml	300–450 γ/100 ml	+
Iron Deficiency	<50 γ/100 ml	often >450 γ/100 ml	0
Iron Overload	>180 γ/100 ml	Normal or diminished, and completely or almost completely saturated	+++

Not very much is known about the changes which occur in myoglobin and the various metalloenzymes of iron Conflicting results have been reported about decreases in myoglobin in experimentally induced deficiency For many years workers have held the belief that cellular iron enzymes did not become depleted even if the hypochromic anemia was severe Recently however, Beutler demonstrated marked diminution in the cytochrome C

content of the liver and kidneys of rats made iron deficient by a combination of bleeding and an iron-poor diet.[30] Catalase in the erythrocytes of patients with iron deficiency anemia, however, shows no significant change from normal values.

4. *Utilization.*—The amount of iron utilized for hemoglobin synthesis per day in a normal adult is approximately 20–25 mg. This value can be calculated as follows:

(*a*) A man with a blood volume of 5,000 ml. and a hemoglobin level of 15 gm. per 100 ml. has 750 gm. of circulating hemoglobin or 2.55 gm. of circulating hemoglobin iron (Hb multiplied by 0.34 per cent).

(*b*) The normal life span of the red cell is about 120 days, so 2.55 gm./120 or 21 mg. of iron would be required daily to replace the catabolized hemoglobin.

A normally functioning marrow can increase its production of red cells and of hemoglobin by a factor of approximately 6 times under maximal stimulation; therefore, as much as 100 to 125 mg. of iron could be used for hemoglobin synthesis per day. Turnover rates for the iron in myoglobin and the iron-containing respiratory enzymes are unknown.

In order to estimate iron utilization for hemoglobin synthesis, two radioactive measurements have been made.

(*a*) Plasma iron turnover rate (PITR). When a tracer dose of labeled iron is bound to transferrin and injected intravenously, half of the radioactivity normally leaves the plasma in 80 to 120 minutes (T ½). From this figure, the serum iron value, and the total plasma volume, the PITR may be calculated. It is rapid in iron deficiency and whenever erythropoiesis is accelerated and is less than normal whenever erythropoiesis is depressed.

(*b*) Utilization of the tracer dose for hemoglobin synthesis. Tagged hemoglobin can be identified in the peripheral blood within 4 to 8 hours; from 70 to 100 per cent of the injected dose is found in circulating hemoglobin within 7 to 14 days. The red cell iron turnover rate may then be calculated by multiplying PITR times the fraction of the tracer dose used for hemoglobin synthesis. These technics have their greatest value in studies of the pathogenesis of various anemias and need not be discussed further here.[20, 23, 31, 32]

Ferrokinetic studies indicate that most of the iron used by the developing red cell for hemoglobin synthesis comes from the transferrin in plasma.[22, 24] Bessis and Breton-Gorius, however, have recently demonstrated an alternative pathway.[6] When histiocytes in the marrow digest phagocyted erythrocytes, the released iron is converted within the cytoplasm of the phagocyte to ferritin and transferred by a process of pinocytosis to the cytoplasm of surrounding erythroblasts. The ferritin then finds its way to the mitochondria of the nucleated red cell where the iron is presumably changed to a form in which it can combine with protoporphyrin to make heme.

5. *Conservation.*—The avid way in which the body conserves and reutilizes iron is an important characteristic of iron metabolism. Mention has already been made of the fact that a normal adult catabolizes enough hemoglobin each day to release 20 to 25 mg. of iron. If this amount were excreted, the iron requirement would be enormously increased and would

far exceed the 0 6 to 1 5 mg of dietary iron absorbed Actually, more than 90 per cent is conserved so that it can be used over and over again Iron released from cells that die anywhere in the body is presumably handled and conserved in a similar manner

6 *Iron Transfer to the Fetus* —Recent studies indicate that the fetus has a highly effective acceptor system for assimilating iron Iron from the maternal transferrin is transferred to the placental tissue, to the fetal transferrin, and then to the fetal tissues This pathway seems to be a one-way street, capable of operating effectively against increased maternal requirements for iron and even in the face of maternal iron deficiency During the last trimester of pregnancy, it may account for a transfer of 3 to 4 mg of iron per day to the fetus [33 34]

7 *Excretion* —Current estimates indicate that in temperate climates approximately 0 5 to 1 mg of iron is lost from the body each day in feces, urine, and sweat [5] These figures have been obtained either by direct chemical analysis or by measuring the excretion of radioiron and calculating total excretion from that value In either case, technical difficulties are so great that the data must be regarded as providing reasonably close approximations only Much of the iron lost is contained in cells desquamated from mucosal surfaces or from the skin, in blood cells found in excreta, etc It has been estimated, for instance, that 50 to 80 grams of mucosal cells are exfoliated from the intestinal tract daily Another portion of fecal iron comes from bile since not all of the iron in bile is reabsorbed from the gut Whether a true process of intestinal excretion also exists is unknown There is particular uncertainty about the magnitude of the dermal loss of iron, with some workers contending that a value of less than 0 5 mg per day is too low for hot, moist climates [36] They point out that a high proportion of the iron in sweat is derived from desquamated cells of the skin, that a film of sweat on the body increases friction between clothes and the skin and that more skin is consequently rubbed off in tropical countries They suggest that the dermal loss in tropical climates may total several milligrams of iron per day If that contention proves to be correct, dermal loss will have to be accepted as an important contributing factor in the development of iron deficiency

Menstrual blood flow must also be regarded as a form of iron excretion The normal menstrual flow is approximately 35 to 70 ml of blood per period At a hemoglobin level of 14 grams per 100 ml, that amount of blood would contain 16 to 32 mg of iron Spread evenly over the 28 days of the menstrual cycle, the average daily loss would amount to about 0 5 to 1 0 mg per day

Finch approached the problem of measuring iron excretion by injecting Fe^{55}, an isotope with a relatively long half-life intravenously into a number of normal subjects and then measuring iron turnover of total miscible body iron during a period of 5 years His values were 0 61 mg per day in men 0 64 mg per day in non-menstruating women, and 1 22 mg per day in menstruating women [37] The agreement between these figures and the above estimates is surprisingly close

The iron needed to support a mother during a normal pregnancy can be stated only in rough terms The maternal organism contributes about

500 mg. to the fetus. An additional amount of iron is lost in the placenta, the lochia, and in hemorrhage at the time of delivery. On the other hand, the absence of menstruation for 12 to 15 or more lunar months provides a saving which reduces the net loss to a figure somewhere in the neighborhood of 300 to 500 mg.

8. *Iron Required for Growth.*—The iron required for growth during infancy and childhood obviously varies with the rapidity of growth at different periods. If a normal male has 0.5 gm. of iron in his body at birth and 5 grams when he stops growing at the age of about 20, he must accumulate during these 20 years roughly 4.5 grams of iron, or 225 mg. per year, or an average of about 0.6 mg. per day. Similarly, if a normal girl has 0.5 gm. of iron at birth and 4 grams when she stops growing at the age of about 15, she must have accumulated 3.5 grams of iron, or about 230 mg. per year, or an average of about 0.6 mg. per day. For the growing child, therefore, about 0.6 mg. of iron per day must be absorbed over and above that lost or excreted in order for a positive balance to be maintained.

9. *The Development of Iron Deficiency.*—If the data and calculations presented provide a reasonable approximation of the normal iron balance, then: (*a*) absorption of 5 to 10 per cent of the food iron in an average diet of 12 to 15 mg. would lead to the retention or assimilation of 0.6 to 1.5 mg. of iron per day; (*b*) the normal male with his total iron loss of less than 1 mg. stays in equilibrium without difficulty; but (*c*) the normal female during her active sexual life is in a precarious state of iron balance because of her additional loss of about 0.5 to 1 mg. Fe per day in menstrual blood; (*d*) the developing child because of his added needs to support growth and his expanding blood volume is also in a precarious state of balance. It is easy to understand, therefore, why iron deficiency anemia is much more common in growing children and in menstruating women than in adult males or postmenopausal women.

The effect of dietary deficiency or of poor absorption in adults should be examined in more detail. Deficient diets are usually associated with a low intake of animal protein and a high intake of cereals—the kind of diet from which iron assimilation is not likely to be high. Persons whose diets contain only 8 to 10 mg. of food iron per day would not be likely to absorb much more than 10 per cent of their food iron, therefore, even though they are deficient. The normal female with her usual loss of 1 to 2 mg. per day would gradually tend to become deficient, but the adult male might even remain in balance.

The calculations in Table 19, based on two hypothetical patients, an adult male and a postmenopausal woman, demonstrate that if these two persons each excreted 1 mg. of iron per day and absorbed none at all, periods of six and four years, respectively, would pass before they became deficient enough to have only 7.5 mg. of hemoglobin per 100 ml. These figures ignore the evidence that as patients become deficient in iron they excrete smaller amounts of the metal.

Similar considerations would hold for persons with steatorrhea or intestinal pathology which would cause a serious absorptive defect.[7]

On the loss side one should note that deficiency can be produced by chronic hemorrhage of only minor degree. The average woman, even when

TABLE 19 —CALCULATION OF TIME REQUIRED FOR DEVELOPMENT OF IRON DEFICIENCY ON NUTRITIONAL GROUNDS ALONE IN TWO HYPOTHETICAL PATIENTS

	Adult male *Hb 15 Gm /100 cc* *Bl vol 5000 cc*		Post menopausal woman *Hb 14 Gm /100 cc* *Bl vol 4000 cc*	
A When Normal				
Total Hb iron	2500 mg		1900 mg	
Storage iron	1000 mg		500 mg	
Total		3500 mg		2100 mg
B After development of Fe deficiency (Hb of 7 5 Gm /100 cc)				
Total Hb iron	1250 mg		950 mg	
Storage iron	0 mg		0 mg	
Total		1250 mg		950 mg
Deficit in Hb and storage iron (with this degree of hypochromic anemia)		2250 mg		1450 mg
Time required to produce deficiency if no iron is absorbed and 1 mg excreted per day		2250 days (6 3 yrs)		1450 days (4 yrs)

medically trained is usually unaware that her menstrual flow is abnormal if it is increased from the normal range of 35 to 70 ml. to a level of 100 to 150 ml. or more. Yet such an increase brings about a menstrual loss of 2 to 3 mg. of iron per day when it is spread equally over the menstrual cycle. Similarly when an individual with a normal hemoglobin level bleeds to the extent of only 2 to 4 ml. per day he loses about 0.8 to 2 mg. of iron per day—an amount great enough to throw him into a negative balance unless his absorptive mechanism is very efficient. In the past clinicians have felt that chronic gastrointestinal hemorrhage of even this minor degree could be detected with routine laboratory tests but that probably is not correct. When blood containing radioactive hemoglobin iron is fed, the isotope is absorbed about as well as it is from other foods.[7] The hemoglobin, therefore, must be digested in large part if it is lost high in the intestinal tract and is present in only moderate amounts. When one is confronted with a man or a postmenopausal woman who has hypochromic anemia but no detectable blood loss the chances are overwhelming that the patient either bleeds intermittently and does not happen to be doing so during the time of examination or that he is losing small amounts of blood high in the intestinal tract which are digested and not detected by clinical laboratory methods. The only other possibility is that the diet has been deficient or absorption defective over a very long period of time—5 to 10 years. However poor diet or poor absorption when coupled with normal growth or normal menstrual loss may readily induce iron deficiency. One should also not ignore the fact that blood transfusion services use millions of pints of blood in the United States per year and every donation costs the donor from 200 to 250 mg. of iron spread throughout the year, that amounts to about 0.6 mg. per day.

10. *Iron Requirement.*—The recommended dietary allowances for iron of the Food and Nutrition Board (Table 20) are rough approximations but are probably adequate for healthy persons in the United States. Information about the absorption of iron from foodstuffs other than those common in the American diet, and about dermal losses of iron in tropical climates is too fragmentary to apply these recommendations to other areas.

11. *Iron Overload.*—Excessive accumulation of iron in man has been observed under four circumstances: (a) in idiopathic hemochromatosis, (b) in transfusion hemosiderosis, (c) after prolonged iron therapy, particularly in patients whose erythropoietic rate is accelerated, and (d) among Bantu natives who consume diets containing as much as 200 mg. of iron per day (much of the iron being derived from kettles used in the preparation of food).[5,39] In addition iron overload has been produced experimentally in animals by transfusions or by injection of inorganic iron over protracted periods of time.[40]

In all instances of naturally occurring iron overload the iron must obviously get into the body by absorption from the gastrointestinal tract. If absorption exceeded needs by only 2 or 3 mg. per day, however, the net accumulation would total 0.7 to 1.0 gram per year. Excess absorption does not have to be great, therefore, in order to account for an overload in an adult of 25 or more grams of iron. In all forms the transferrin is either normal or slightly reduced and the plasma iron is increased to levels

which saturate or nearly saturate the transferrin present. The basic question about iron overload may be stated simply: does the excess iron itself cause toxicity responsible for the changes observed in hemochromatosis, or are other factors involved?

Idiopathic hemochromatosis is a moderately rare disease; it occurs predominantly in males, may possibly be the result of an inborn error of metabolism, and is characterized in its fully developed form by cirrhosis of the liver, bronzing of the skin, diabetes mellitus (bronze diabetes), and certain other abnormalities, particularly of endocrine organs. The iron is largely deposited within the parenchyma of cells, and tissues seem to have an avidity for the metal. In contrast, the other forms of iron overload are often not associated with cirrhosis of the liver; diabetes is rare, and distribution of iron occurs largely in the reticulo-endothelial cells as hemosiderin rather than within the parenchyma.[40] Not until iron deposits are heavy does the element appear in epithelial tissues in significantly greater amounts. Even among the Bantu who may also have cirrhosis of the liver, no constant correlation is found between the degree of fibrosis and the amount of iron in the liver. It is true that an occasional patient with hypoplastic anemia and transfusion hemosiderosis will develop diabetes and hepatic cirrhosis, but the fact that so many patients do *not* strongly suggests that other factors must be involved. Dogs with iron overload for as long as 7 years showed no fibrous reaction in any tissue and handled glucose normally.[40] There is little evidence to suggest, therefore, that large amounts of tissue iron are toxic so long as the iron remains predominantly in reticuloendothelial cells, although not all workers would be in agreement with this statement.[25] When iron has a parenchymal distribution, as in idiopathic hemochromatosis, then hepatic cirrhosis, bronze diabetes, and the other abnormalities of hemochromatosis appear. Whether the parenchymal iron causes these effects, or whether other metabolic abnormalities are responsible both for the pathologic changes and the parenchymal distribution of the iron remains unanswered.

Iron Deficiency—Hypochromic Microcytic Anemia.—The frequency of iron deficiency and of its hypochromic microcytic anemia has already been emphasized. In some countries 30 to 50 per cent of the population may be affected. Within any population group, incidence is always greatest among infants and children, and among women during the years when they are menstruating and bearing children.

1. *Laboratory Manifestations.*—Hypochromic microcytic anemia is the hallmark of fully developed iron deficiency, but does not appear until iron stores are exhausted. The milder, and possibly the more common form of iron deficiency anemia may be normocytic and normochromic, or only slightly hypochromic.[41] Relatively few studies have been made in which the development of the deficiency has been traced, but these indicate that the train of events might be roughly as follows: depletion of iron stores, rise in the transferrin levels, fall in serum iron, fall in the hemoglobin and appearance of hypochromia. There must be many variations in this pattern. For instance, frank hemorrhage occurring early in the course of what otherwise would be chronic blood loss (as from a peptic ulcer) would certainly cause the serum iron to decrease before tissue stores would be

exhausted. Iron stains done on aspirated bone marrow have provided a valuable even though rough index of storage iron.[9]

In fully developed iron deficiency and anemia the red blood corpuscles are pale. The normal central clear area of erythrocytes, caused by their biconcave shape, may be so large that it appears as if there were only a rim of hemoglobin about the margin of the cell. The mean corpuscular hemoglobin concentration is less than 32 per cent (normal 33 to 37 per cent). There is usually microcytosis and considerable variation in size and shape of the cells (mean corpuscular volume less than 80 cu. microns). Total hemoglobin is reduced to a greater degree than is the total red cell count. The latter is only rarely less than three million cells per cu. mm. and is often within the normal range, whereas the hemoglobin may be less than 5 gm. per 100 ml. of blood. One may find a red blood cell count of nearly 5 million cells with only 6 or 7 grams of hemoglobin. Reticulocytes are usually normal or slightly reduced in number. The leucocyte count is often normal, but a slight leucopenia may be found. In the latter case the differential may show a relative lymphocytosis and an absolute granulocytopenia. Hypersegmented neutrophils are sometimes present; there are no other morphologic changes in the leukocytes. Platelets ordinarily are not affected but on rare occasions may be reduced moderately in number. The bone marrow is hyperplastic, particularly for nucleated red blood cells, most of which are fairly mature normoblasts.

Achlorhydria is common. More than two thirds of all cases fail to secrete free hydrochloric acid after an alcohol or food test meal and more than half fail to do so even after histamine. The plasma iron value is less than 50 micrograms per 100 ml. (normal 50–180 micrograms per cent). The transferrin is increased to levels sufficient to raise the serum iron binding capacity usually to above 450 micrograms per cent. Iron stains on aspirated bone marrow are almost always negative for hemosiderin—occasionally a few small granules may be found.

2. *Differential Diagnosis.*—Whenever hemoglobin synthesis is defective hypochromia of the formed red cells may be found. Such defects would occur not only with iron deficiency but abnormalities of protoporphyrin and globin synthesis as well. As a result hypochromia may be found in the absence of iron deficiency under the following circumstances: the thalassemia syndromes, severe protein deficiency (Kwashiorkor), vitamin B_6 deficiency, hereditary hypochromic anemia, and idiopathic refractory sideroblastic anemia.[4] Fortunately, all of these other forms of hypochromic anemia are rare in the United States except for the thalassemia syndromes and all are associated with normal or increased serum iron levels, no elevation in transferrin and normal or increased amounts of hemosiderin in the bone marrow.

3. *Clinical Manifestations.*—Symptoms are insidious in their onset. The anemia may develop so gradually that it interferes only moderately with work efficiency. Many of the complaints are those common to all anemias: weakness, fatigability, pallor, dyspnea on exertion, palpitation, headache and a feeling of "dead tiredness." About one-third of cases have a sore tongue or sore mouth but the discomfort is rarely as great as in pernicious anemia. An occasional patient will have fissures or cheilosis at the corners

of the mouth, but the change is probably not related directly either to the anemia or to the iron deficiency. Rarely, dysphagia is a prominent complaint. The co-existance of dysphagia and hypochromic anemia has aroused considerable interest, and is frequently referred[9] to as the Plummer-Vinson syndrome. Vague gastrointestinal complaints such as a capricious appetite, flatulence, epigastric distress, and constipation are fairly common. Many patients have numbness and tingling of their hands and feet, but these symptoms are not so troublesome as in pernicious anemia. Weight loss does not occur as a manifestation of the anemia *per se*.

Pallor of the skin, mucous membranes, and nail beds is proportional to the reduction in hemoglobin. Vitiligo may be present. The sclerae are pearly-white. About 40 per cent of adults with hypochromic anemia have some degree of papillary atrophy of the tongue. The heart is often slightly enlarged—functional murmurs are not infrequent. The liver may be slightly enlarged and in about one-third of cases the tip of the spleen can be felt at the costal margin. Slight dependent edema may often be found. The neurological examination is almost always normal. The fingernails in many patients are brittle and show a longitudinal ridging and flattening. This latter change may be so advanced as to make the nails concave instead of convex; they then have a "spoon-shaped" appearance (koilonychia).

The epithelial changes (in the tongue, koilonychia, dysphagia), the paraesthesias, and the gastrointestinal symptoms improve after iron therapy, but defective secretion of gastric acid often persists. Recent evidence indicates that the gastric mucosal lesions of iron deficiency often precede the development of hypochromic microcytic anemia and do not improve after therapy.[43]

4. *Diet and Prevention of Iron Deficiency.*—Because of the relatively high iron requirement of growing children and of women during the period of their active sexual life, an adequate dietary intake of iron is particularly important to maintain a positive balance among these two groups. Infants maintained on a low iron milk diet without supplements after the first six months of life have a high incidence of iron deficiency. Famines or the food shortages which frequently occur during wars cause a striking increase in hypochromic anemia among women and children.[3] When the food deprivation is maintained over a period of years, or when absorption is chronically defective, hypochromic anemia may even develop among adult males free of any blood loss.

For all ordinary needs, the dietary allowances recommended by the Food and Nutrition Board (Table 20) are adequate. A daily intake of 15 mg. of iron is not difficult to provide as long as the diet includes one egg and one serving of meat per day. One serving of red meat, one egg, a pint of milk, four slices of whole wheat or of "fortified" bread, and two servings of vegetables will supply at least two-thirds of that amount. One hundred grams of liver contain nearly 8 mg. of iron.

Persons who lose blood chronically, who serve regularly as blood donors, and women who have frequent pregnancies may need supplements of inorganic iron in order to prevent the development of iron deficiency. Full therapeutic doses of iron are not necessary. The daily administration of

0.3 gm. of a ferrous salt during the period of increased requirement is adequate.

5. *Treatment of Hypochromic Microcytic Anemia.*—Once iron deficiency has developed, dietary management alone is not sufficient and iron must be given therapeutically. Adequate therapy must not only correct the deficiency but also treat its cause. Increased menstrual flow, occult loss of blood from the urinary or gastrointestinal tracts or defective absorption must be searched for with diligence and corrected if possible.

TABLE 20.—RECOMMENDED DIETARY ALLOWANCE OF IRON

(Food and Nutrition Board, National Research Council)

	Iron mg
Man (154 lb., 70 kg.)	10
Woman (128 lb., 58 kg.)	12
Pregnancy (latter half)	15
Lactation	15
Children	
Under 1 year	6
1-3 years	7
4-6 years	8
7-9 years	10
10-12 years	12
Over 12 years	15

Iron is administered orally, preferably in the form of ferrous salts because they are more efficiently absorbed and can be administered in smaller amounts than the corresponding ferric forms. Either ferrous sulfate or ferrous gluconate is satisfactory. Tablets are marketed which may be administered as follows:

Exsiccated ferrous sulfate [$(FeSO_4)_2 \cdot 3H_2O$]	0.2 gm./tablet One 4 times daily
Crystalline ferrous sulfate ($FeSO_4 \cdot 7H_2O$)	0.32 gm./tablet One 4 times daily
Ferrous gluconate	0.32 gm./tablet One 4 times daily

The dosage is built up gradually because patients tend to develop a tolerance for iron and have less gastrointestinal disturbance (nausea, heavy sensation in epigastrium, diarrhea) when this is done. The first day, 1 tablet is taken after breakfast and 1 after the evening meal. The second day a tablet is also taken after the mid-day meal. On the third day a fourth tablet is added at bedtime. Some patients apparently have fewer gastrointestinal symptoms from ferrous gluconate than from other forms of iron.

In order to understand the rationale of this dosage schedule and the fact that iron therapy must be continued for six to eight weeks, it is necessary to present the following quantitative considerations. About five to seven days after the start of iron therapy the reticulocytes begin

to rise, they reach a peak level of about 10 to 15 per cent usually between the tenth and fourteenth days, and then fall in seven to ten days to normal levels. The height of the reticulocyte level is inversely proportional to the original hemoglobin value. The hemoglobin begins to increase on about the seventh to tenth days and regenerates at the following average rates:

0.2 to 0.3 gm./100 ml. blood/day with initial Hb. less than 7.5 gm. per cent
0.1 to 0.2 gm./100 ml. blood/day with initial Hb. more than 7.5 gm. per cent

As the hemoglobin approaches normal levels, the rate of increase slows, from four to eight weeks are required before normal values are attained.

Since the maximum rate of hemoglobin increase in response to iron therapy seems to be about 0.3 gm./100 ml. of blood per day, the daily oral dose should be great enough to permit the synthesis of that amount of hemoglobin: 0.3 gm./100 ml. or 15 grams/blood volume of 5 L. Hemoglobin contains 0.34 per cent iron, therefore, 15 gm. of hemoglobin equals about 50 mg. of iron. There is evidence to indicate that iron deficient patients absorb only about 20 per cent of ordinary oral doses of soluble ferrous salts, so that the required dose would be about 50 × 5, or roughly 250 mg. of actual iron. The above recommended doses of ferrous sulfate and ferrous gluconate provide approximately this amount.

Even if the rather high absorptive rate of 50 mg. per day is continued, six to eight weeks are usually *required for complete correction* of the deficiency. A woman, for instance, with a severe degree of iron deficiency anemia may have only 5 gm. of hemoglobin per 100 ml. If her normal hemoglobin level is 14 gm./100 ml. and her blood volume 5 L., she must increase her hemoglobin a total of 9 gm. per 100 ml. or 450 gm. for her whole blood volume. This amount of hemoglobin contains approximately 1.5 gm. of iron. One should also, however, provide her with an additional 0.5 to 1 gm. in order to replenish her tissue stores. It would take her roughly forty to fifty days to absorb 2 to 2.5 gm. of iron at the rate of 50 mg. per day.

For infants and small children, the iron may be furnished as an elixir of ferrous sulphate or ferrous gluconate. The total daily dose should be divided into three or four parts and be sufficient to provide 0.3 to 0.4 gm. of ferrous sulphate or 0.45 to 0.6 gm. of ferrous gluconate.

The pharmaceutical market has been flooded with iron preparations which also contain molybdenum, cobalt, copper, liver extract, and various vitamin combinations. These proprietary preparations, however, are more expensive and none has been proven to be superior to iron alone. Their use is unscientific and should be avoided.

There are exceptional patients who are unable to tolerate oral iron therapy or who are unable to absorb the metal in adequate amounts. These are patients with ulcerative colitis, regional ileitis, ileostomy or colostomy, intestinal shunts, or steatorrhea. Very rarely, a patient with no demonstrable intestinal abnormality may have so much nausea and diarrhea with oral iron therapy that she refuses to continue it. In these isolated instances parenteral iron therapy is of great value and may be provided by intramuscular injections of iron dextran. Solutions of this compound are commercially available containing 50 mg. of elemental iron per ml. The

first injection should be 1 ml, thereafter daily doses of 2 or 2.5 ml may be given. Care should be taken to insert the needle into the injection site of the buttocks through a zig zag path to avoid leakage back through the needle track and consequent permanent staining or tatooing of the skin. Mild allergic reactions have been reported as one would expect since such reactions occur to dextran but fortunately are infrequent.[44] A total dose of 1.5 to 2 gm. should not be exceeded. Therapeutic responses are excellent.

COPPER

Copper functions in mammalian tissues as a component of various metalloenzymes and proteins required for normal erythropoiesis, bone formation and for a number of oxidation reduction reactions. It also has an effect on iron metabolism. The several copper containing enzymes and proteins already identified are probably only representative of many others waiting to be isolated, but even for those now known the exact mechanism and site of action are often poorly understood. Copper deficiency has been produced experimentally, has been observed among cattle and sheep grazing on copper-deficient soils but has never been clearly demonstrated in man. Much interest has recently been focused on the abnormalities of copper metabolism in hepatolenticular degeneration (Wilson's disease). Several excellent reviews of copper metabolism and nutrition have been published,[45–49] they should be consulted for more detailed discussion and bibliographic documentation.

Metabolism and Human Requirements.—The total body of an adult contains approximately 100 to 150 mg. of copper distributed in all tissues in a concentration varying from about 2 to 8 micrograms per gram wet weight. While highest concentrations are found in liver and the central nervous system, muscles and bone because of their great mass have 50 to 75 per cent of the total amount. Unless the intake is abnormal, copper does not seem to be preferentially accumulated by any tissue.

The average adult in the United States ingests from 2.5 to 5 mg. of copper per day but can maintain a positive balance on as little as 2 mg. per day. The copper content of food depends to a large extent on the amount in the environment; the metal is so widely distributed in foods, however, that any calorically adequate diet will almost certainly provide at least 2 mg. per day. The daily requirement for children is about 0.05 to 0.1 mg. per kilogram of body weight. Copper is probably absorbed from the upper portion of the small intestine; there is little information about the comparative retention of organically bound versus inorganic copper, cupric versus cuprous forms, the possible augmenting effect of deficiency on absorption and the mechanism of absorption.

Copper is transported in the plasma. Whole blood contains about 100 micrograms per 100 ml. distributed approximately equally between plasma and erythrocytes. The amount tends to be quite constant particularly in red cells; serum values, however, rise during pregnancy and in many disease states: infectious diseases, myocardial infarction, Laennec's cirrhosis, hemochromatosis, leukemia, malignant lymphomas, certain malignant tumors, sickle cell anemia, thalassemia, untreated pernicious anemia,

aplastic anemia, and even schizophrenia. Low values for serum copper will be discussed under "Copper Deficiency in Man." Two forms of copper are found in plasma: a small portion (about 5 per cent), probably the active transport fraction, loosely bound to plasma proteins, and ceruloplasmin (about 95 per cent), a blue copper-containing $alpha_2$ globulin with a copper content of 0.32 per cent, 8 atoms of copper per molecule, and a molecular weight of about 151,000.[50, 51] Normally, there are 15 to 30 mg. of ceruloplasmin per 100 ml. of plasma. It has been implied that the physiologic function of ceruloplasmin is related to its oxidase activity. The recent demonstration, however, that the copper can be reversibly dissociated to yield an apoprotein is consistent with the possibility that ceruloplasmin may function by reversibly releasing and binding copper at various sites in the organism.[5] Ceruloplasmin is chiefly responsible for the increases described in the various diseases above; it is reduced in patients with Wilson's disease. When a small amount of radioactive copper is given orally to normal subjects, plasma radiocopper curves show a transient initial rise in the direct reacting fraction followed by a decline; a secondary gradual rise in the Cu^{64} of ceruloplasmin then occurs. Red cell copper is probably also made up of at least two fractions: a labile form which seems to be in equilibrium with the smaller (direct reacting) fraction in plasma, and a stable form (hemocuprein or erythrocuprein, mol. wt. 35,000, 0.34 per cent copper, 2 atoms Cu per molecule). This stable fraction exchanges rather slowly with the labile component and accounts for more than 80 per cent of the copper in red blood cells. The function of erythrocyte copper is not known, but nucleated red cells contain a small amount of *delta* aminolevulinic acid dehydrase, a copper containing enzyme active in the synthesis of protoporphyrin.[53]

There is little information about the chemical composition of the copper stored in tissues, its turnover rate, the amount used for different enzymes, or in many instances the site of action of the enzymes. Several liver copper proteins including hepatocuprein (mol. wt. 35,000, 0.34% copper) have been isolated; they may, however, represent specific fractions of liver copper rather than storage forms. Increased hepatic concentrations are found in thalassemia, hemochromatosis, and cirrhosis. The concentration of copper also increases in the liver during fetal life to a level 5 or 10 times that found in adults; after birth it slowly decreases until adult values are attained sometime between the ages of 5 and 15 years. The extra copper probably serves as a reserve during the nursing period when the intake is low, but it may also be related to the period of maximum growth.

Copper balance is achieved by adjustments in the excretion rate to accommodate the amount absorbed. This control is operative only within certain limits; grazing animals feeding on pastures of high copper content may accumulate in their livers ten to twenty times the normal concentration.[46] The chief channel of copper excretion is via the intestinal tract, the metal reaching the lumen largely through the bile but also in part by true excretion from the intestinal wall. Additional amounts are lost in urine, sweat, and menstrual flow. The urinary excretion is largely independent of the intake and averages less than 70 micrograms per day. The average menstrual loss is about 0.55 mg. per period.[54]

Copper Deficiency—*In Animals* —Experimentally produced copper deficiency in rats, rabbits dogs and swine is characterized by a slower rate of growth and by the development of anemia hypochromic microcytic in type except that in dogs it is normocytic and normochromic [48 49 55] The plasma copper decreases early during induction of the deficiency followed by a decrease in erythrocyte copper a fall in the plasma iron to levels as low as occur in iron deficiency and a rise in the iron binding protein (transferrin) Normoblastic hyperplasia is found in the marrow The administration of iron alone (even parenterally) has no effect but copper leads to rapid recovery from the anemia and promptly corrects the growth defect Recent studies in copper deficient swine indicate that the deficiency causes decreased absorption of iron from the intestinal tract interferes with the utilization of iron for hemoglobin synthesis and causes defective erythropoiesis The red cells produced have a shortened survival time, the anemia therefore is partly hemolytic but results also from failure of the copper-deficient marrow to accelerate red cell formation enough to compensate for the hemolysis

The naturally occurring copper deficiency observed in cattle and sheep grazing on copper-low soils differs from the induced deficiency described above in that there seems to be no interference with iron absorption high tissue concentrations of iron may actually accumulate The animals become anemic and lose weight they develop diarrhea fragile bones ataxia defective keratinization loss of haircoat color decreased reproductive capacity, fetal abnormalities and sudden death Atrophic lesions are often found in the myocardium along with demyelinization of portions of the central nervous system The disease occurs in widely scattered peat and muck soil areas Australia New Zealand Northern Europe India South Africa, Peru and in parts of Florida Its recognition as copper deficiency plus the demonstration that it could be prevented or cured by treating the soil or forage with copper has been of great economic importance The problem was not so simply resolved however because the amount of copper which had to be added to soils differed widely in various areas Additional work then showed that the ingestion of other elements particularly molybdenum which became concentrated in certain pastures adversely influenced copper metabolism That astute observation discussed in the section on molybdenum below pointed out the importance of interrelationships among certain of the trace elements

The varied manifestations of copper deficiency in animals indicate that the element serves important functions in iron metabolism bone marrow function growth bone development pigment formation in maintaining (at least in ruminants) the myelin of the central nervous system etc [1 49] It probably exerts these effects as the prosthetic group in certain enzymes or as an enzyme activator but our knowledge is very limited Butyryl coenzyme A dehydrogenase is a copper enzyme capable of catalyzing the first step in the oxidation of fatty acids with three to eight carbon atoms Copper is linked to purine metabolism by the claim that uricase is probably a copper protein Tyrosinase a copper enzyme is active in the formation of melanin Copper catalyzes the closure of the sulfhydryl groups in the keratin molecule to form disulfide bridges necessary for the normal kinky

structure of wool It may play a role in the cytochrome oxidase comple in mammalian tissues, possibly by stimulating synthesis of the hem prosthetic group in cytochrome oxidase [66] A copper protein has bee detected in milk, but as in the case of *ceruloplasmin, hemocuprein, an* hepatocuprein, no physiologic function for it has been identified

In Man —Copper deficiency has never been observed in man Becaus *of the hypocupremia characteristic of experimentally* induced copper de ficiency, the low plasma copper levels found in some patients with neph rosis (urinary loss of ceruloplasmin) and sprue have been of interest but in no instance has the diagnosis of copper deficiency been established [48, 4] Wintrobe and his associates fed diets identical to those used to produce deficiency in growing pigs to two infants for four and five months, respec tively, without obtaining any evidence of copper deficiency [47] Claims that the combined administration of copper and iron in the treatment of hypo-chromic anemia may at times be more effective than iron alone have been poorly controlled and have not been confirmed by more critical studies

Hepatolenticular Degeneration (Wilson's Disease) [57–59]—In Wilson's disease the concentration of copper is increased about tenfold in liver, the involved areas of the brain, and all tissues studied except heart muscle, skeletal muscle, lung and erythrocytes A marked decrease in cerulo-plasmin causes the total plasma copper level to be low the direct reacting fraction is actually increased (11 to 50 micrograms per 100 ml) over the values found in normal plasma (0 to 17 micrograms per 100 ml) but not enough to compensate for the low level of ceruloplasmin These patients may have a specific inherited inability to synthesize ceruloplasmin at a normal rate [59] The high tissue concentrations result from an increased absorption of dietary copper, Scheinberg and Morell have presented theoretical considerations explaining how the low plasma ceruloplasmin could bring about greater than normal absorption of copper [60] The copper content of spinal fluid is high If the lesions in the liver and the lenticular nuclei are the consequence of the high deposition of copper in these tissues, as has been suggested, the mechanism of the toxic effect has not been explained Urinary excretion of copper is increased to levels of 100 to 1000 micrograms per day The amino-aciduria also characteristic of Wilson's disease has been attributed to decreased tubular reabsorption of certain amino acids and peptides because of the renal accumulation of copper Whether there are disturbances in the excretion of copper into bile has not been determined Some therapeutic success has been achieved by long term therapy aimed at decreasing the gastrointestinal absorption of copper (oral potassium sulfide), and at increasing urinary excretion through the use of copper chelating agents (BAL, calcium disodium salt of ethylenediaminetetraacetic acid) and a high protein diet (increased excre-tion of amino acids with copper chelated to them)

Effect of Excessive Amounts of Copper —Chronic ingestion of more copper in fodder than is necessary to maintain nutritional balance in sheep leads to the accumulation of ten to twenty times the normal hepatic concentration [46] The animals suffer no apparent ill-effects until suddenly a large amount of the excess copper is liberated into the blood stream A hemolytic crisis is produced, hemoglobinuria and jaundice develop and the

animal often succumbs Over 60 per cent of the circulating red cells may be destroyed during the crisis Atrophy of the liver may occur after several attacks For some unknown reasons the syndrome of chronic copper poisoning is enzootic among sheep grazed in certain areas of eastern Australia Large amounts of copper accumulate in the tissues of these animals even though the pasture contains only normal amounts of the metal Cattle apparently accumulate toxic amounts of copper less readily but a similar type of hemolytic jaundice has been observed when they do In rats and rabbits hemolytic crises do not seem to be a characteristic of chronic copper poisoning It is interesting that a severe hemolytic anemia occasionally precedes the onset of other clinical manifestations in Wilson s disease, no determinations of plasma copper during such episodes have been reported in the literature

COBALT

Cobalt serves its only known biological function as the metallo-element in vitamin B_{12} an accessory food factor which originates as a metabolic product of certain micro organisms Vitamin B_{12} contains about 4 per cent cobalt and is thought to function as a coenzyme in nucleoprotein synthesis Cobalt deficiency in animals seems to be purely a deficiency of vitamin B_{12} it can be corrected by injection of that substance but not by cobalt *per se* because animal tissues apparently have no metabolic pathway for using cobalt in the synthesis of vitamin B_{12} Pernicious anemia with its attendant neurological manifestations and certain other megaloblastic anemias constitute the expression of vitamin B_{12} deficiency in man Sheep and cattle raised on cobalt deficient pastures develop a disease which formerly was regarded as a cobalt deficiency but which in reality results because there isn t enough cobalt in the rumen of these animals for bacteria to synthesize the vitamin B_{12} they require [1,46]

Cobalt is also of biological and medical interest because pharmacological doses stimulate erythropoiesis This effect is mediated in part through the increased production of an erythrocyte stimulating substance or substances (erythropoietin) [61] The suggestion has even been made that erythropoietin may contain cobalt There is absolutely no evidence at present however to support that speculation to indicate that the normal production of erythropoietin is related to cobalt or to indicate that a profound deficiency of cobalt would lead to decreased production of erythropoietic stimulating material

Metabolism and Requirement —Cobalt is required for the synthesis of vitamin B_{12} by bacteria in the intestinal tract In ruminants enough synthesis occurs in the proximal portions of the gut so that the vitamin B_{12} formed can be absorbed A total ingestion of 0.07 to 0.08 mg of cobalt per day is close to the quantity that will meet the needs for this synthesis in sheep and probably in cattle as well [46] In animals like man however where the formation of vitamin B_{12} takes place in the colon absorption does not occur or is minimal Cobalt in order to be of nutritional value for the human therefore must be ingested or injected as vitamin B_{12} The human obtains the nutrient largely from animal tissues the animals having

acquired it either as the direct result of microbial synthesis or by the ingestion of other animals. The human requirement for dietary vitamin B_{12} is not known, but in terms of the amount actually absorbed is probably no more than 1 microgram per day. Factors influencing the absorption and excretion of vitamin B_{12} are discussed elsewhere in this volume.

If animals have a need for cobalt other than as vitamin B_{12}, the requirement is certainly very small. Approximately 5 to 8 micrograms of cobalt are supplied daily in a normal human diet. A small portion is absorbed, apparently in the cobaltous valence state; the remainder passes through the intestinal tract. Very little of the absorbed cobalt, or very little of that given parenterally, is retained.[63,64] The chief path of excretion is in the urine; a portion of the small fraction eliminated by the bowel comes from bile. Highest tissue concentrations develop in the liver, kidneys, pancreas, and spleen. The amount found in plasma and erythrocytes is only about 1 microgram per 100 ml.[1]

Cobalt Deficiency.—Evolution of our information about cobalt deficiency in ruminants makes an exciting story.[1,46] Enzootic marasmus or bush sickness had been recognized for many years, but was first shown in 1934 in Australia to be caused by a lack of cobalt. Manifestations differ in various geographic areas depending on the severity of the deficiency and on the occasional co-existence of copper deficiency, but in general are characterized by impaired growth, listlessness, anorexia, progressive emaciation, and varying degrees of anemia. The livers of affected animals are deficient in cobalt but contain excessive amounts of iron. The disease has been observed in parts of Australia, New Zealand, Kenya, Scotland, and the United States. Cobalt by mouth both cures and prevents it; injected cobalt is without effect.

Therapeutic response to liver extract or to vitamin B_{12} in amounts comparable to those used in the treatment of pernicious anemia in man was disappointing. When the dose was increased to about 300 micrograms of vitamin B_{12} per week, however, the response was dramatic. Ruminants apparently have a much higher requirement for the vitamin than do other animals and the bacteria in their rumen are able to synthesize this amount when adequate amounts of cobalt are ingested. A high concentration of molybdenum in the forage interferes with and may actually halt the synthesis of vitamin B_{12} in the rumen of cattle, presumably because of an effect on the metabolism of the micro-organisms in the rumen. Horses and pigs raised on the same deficient areas remain normal because their requirement is much less.

Erythropoietic Stimulating Effect of Cobalt.—Administration of pharmacological amounts of cobalt, either orally or parenterally, will induce a true polycythemia in many species of animals:[46,6] reticulocytosis, elevated erythrocyte and hemoglobin levels, increased total red cell mass and normoblastic hyperplasia in the marrow. This effect is not mediated through vitamin B_{12}; very large doses of that substance do not cause erythrocytosis. It was formerly attributed to the production of cellular anoxia in the marrow by combination of cobalt with—SH groups (*i.e.*, in cysteine, histidine) or by inhibition of certain enzymes (succinoxidase, choline oxidase, cytochrome oxidase, catalase, cholinedehydrogenase,

succinic dehydrogenase). Direct measurement of marrow respiration, however, has revealed no significant abnormalities and cobalt inhibits heme synthesis *in vitro* at levels lower than those required to interfere with oxygen consumption.[66] Recent evidence furthermore indicates (1) that anoxic polycythemia is produced not by marrow hypoxia directly but by increased formation of an erythropoietic stimulating factor or factors (erythropoietin), and (2) that the administration of cobalt also leads to greater production of the same or of a similar erythropoietic factor.[61] Cobalt may induce polycythemia therefore by increasing the formation of erythropoietic stimulating hormones, but it does so in pharmacologic, not physiologic doses. There is as yet no evidence that cobalt is a part of the poorly defined erythropoietin or that it has anything to do under physiologic conditions with maintaining a normal concentration of erythropoietin.

After cobalt is administered, iron absorption is apparently increased and more iron is used for hemoglobin synthesis. Some workers have implied therefore that cobalt has a direct effect on iron metabolism. It seems more likely, however, that the effect is on erythropoiesis and the accelerated erythropoietic rate influences the metabolism of iron. For instance, whenever erythropoiesis is accelerated, iron seems to be better absorbed and it naturally would be used more rapidly when red cell and hemoglobin production is stimulated.

During the past few years the therapeutic value of cobalt in the treatment of human anemias has been extensively studied. A rise in red cell values has been observed in some patients with refractory or hypoplastic anemia, with the anemia of chronic nephritis and with the anemia of infection.[48, 67, 68] The therapeutic doses of cobaltous chloride are rather large (50 to 150 mg. of the salt per day) and frequently cause gastrointestinal irritation; organic complexes currently being tried may be more easily tolerated. While these therapeutic effects are interesting and important, they have little to do with the nutritional aspects of cobalt metabolism and will not be further discussed.

MOLYBDENUM

Molybdenum began to attract attention as a trace element of nutritional importance when it was demonstrated in 1930 that the growth of *Azotobacter* in media containing N_2 as the only source of nitrogen was increased several times by the addition of minute amounts of molybdate. Subsequent work has shown that traces of molybdenum are present in all plant and animal tissues that have been adequately examined.[46] The element now known to be an essential nutrient for many micro-organisms and plants has recently been shown to play some part in animals in the action of several flavoproteins: nitrate reductase, xanthine oxidase, aldehyde oxidase and hydrogenase.[70] Xanthine oxidase contains one atom of molybdenum, the metal probably facilitates the linkage of flavin nucleotide to protein. In the section on Iron Metabolism attention has already been called to the demonstration that xanthine oxidase is of importance in the mobilization of ferritin iron in the liver.[8] No characteristic syndrome of molybdenum deficiency has been recognized in the human or in animals.

Metabolism.—Molybdate is readily absorbed from the intestinal tract.[46] It is distributed in largest amounts in the liver, skeleton, and kidneys, but when administration is discontinued all but a small amount is discharged from the body. Excretion occurs chiefly in the urine but a small amount is also lost in bile. Diets deficient in molybdenum cause a decrease in intestinal xanthine oxidase activity which can be corrected by addition of small amounts of molybdate to the diet.[71]

Rats are able to use 50 to 100 per cent of the molybdenum in most foods for the synthesis of intestinal xanthine oxidase.[7] Foods containing 0.6 part per million (dry weight) of available or enzyme-producing molybdenum activity include legumes, cereal grains, some of the dark green leafy vegetables, and animal organs. Fruits, berries, and most root or stem vegetables have less than 0.1 part per million.

Effects of Chronic Ingestion of Molybdenum.—One of the most interesting nutritional aspects of molybdenum metabolism relates to its interrelationship with copper, particularly in ruminants. As the molybdenum content of forage increases, more copper is required to prevent the development of copper deficiency.[1,46] The mechanism of this effect is not understood, but the inorganic sulfate content of the diet is important in its mediation. If the sulfate is low, high levels of molybdenum may actually lead to an increase in the copper of liver and other tissues. Under these circumstances, the molybdenum may be "fixing" the copper in tissues or antagonizing copper-containing enzymes. On the other hand, if the feed contains an adequate level of sulfate and an increased amount of molybdenum, then copper reserves are depleted and the molybdenum is also rapidly eliminated. Administration of copper causes rapid improvement even when the copper content of tissues is not low. Sulfate seems to reduce the storage of molybdenum and to protect against its toxicity, possibly because of an effect on the permeability of cell membranes to molybdenum.[73]

In monogastric animals like the rat, toxicity from excessive molybdenum is associated with retarded growth and elevation of liver alkaline phosphatase, but copper deficiency is harder to produce. The addition of methionine to whole milk markedly prevents the harmful effects of molybdenum in rats.[74]

FLUORINE

Fluorine has been recognized as a constituent of the skeletal system ever since Morichini in 1803 found fluorides in the bones of a fossil elephant. In 1892 Crichton-Browne suggested that the increased incidence of dental caries in England was due at least in part to a depletion of fluorine in the diet. During the early part of the present century, most of the investigations on this element were directed toward a study of its possible toxic effects. General interest was not aroused until about 1931 when it was discovered that fluorine in drinking water caused mottled tooth enamel. This observation led several communities to change their water supply so as to reduce the fluorine content to a minimum. Several years later when public health surveys were made to observe the lower incidence of mottled enamel in these population groups, the surprising discovery was made that children born after the water supply had been changed showed more

dental caries than did children who had been exposed to the fluorine drinking water. Small amounts of fluorine in drinking water seem definitely to lower the incidence of dental caries. At the present time fluorine's right to be considered an essential trace element is dependent on this observation, whether it is essential to any other function of the body is not known. Available data indicate that the optimum concentration of fluorine in drinking water to prevent dental caries is approximately 1 part per million (ppm); increased amounts cause mottling of the enamel. Much of the knowledge of the relationship between fluorine intake and the prevention of caries has been summarized in publications of the National Research Council,[75] and the American Association for the Advancement of Science.[76]

A. **Importance of Fluorine to the Teeth.**—1. Endemic Dental Fluorosis (Mottled Enamel).—Investigation of mottled enamel began in 1908 when McKay and later Black attempted to find out why residents of Colorado Springs were afflicted with this dental abnormality while people in adjoining communities did not show the change.[76a] It was soon discovered that the teeth of those individuals who had come to Colorado Springs after enamel formation was complete were likewise free of mottling. In two communities not over four miles apart, all of the native children in one town were afflicted while all those in the other village were free of mottling. McKay and Black also made the astute observation that towns in which mottled enamel was common most often derived their water supply from deep wells. Those villages relatively free of the abnormality usually obtained their water from rivers or streams. By 1916 it was clear that the disease was waterborne. In 1925 McCollum and his associates demonstrated that the addition of small amounts of fluorine to the diets of growing rats caused the upper incisor teeth to overgrow and become curved so that they pierced the palate; lower incisors became eroded to the gum line. The teeth in these rats became brittle, opaque, and white. Not until three years later, however, was fluorine identified by three separate groups of investigators as the constituent of drinking water responsible for mottling in human subjects.[76, 77, 78] The designation "chronic dental fluorosis" was given to the abnormality.

Chronic dental fluorosis has been recognized on every continent. Its distribution as recorded by Dean is given in Figure 17.[76a] The West Texas Panhandle region constitutes the largest known region of endemicity in the United States. Concentrations in drinking water of 1 p.p.m. are apparently safe, but the incidence of the disease increases as the concentration in water becomes greater. At 2.5 p.p.m. the incidence is 75 to 80 per cent and at 6 p.p.m. all members of the population show the condition.[78, 79]

Fluorine acts during the period of calcification of the teeth, so that as the teeth erupt they show the characteristic changes. The teeth have dull chalky white patches distributed over the surface, and in some cases the whole tooth surface may present a dead white unglazed appearance (Fig. 18). There may be discrete or confluent pitting of the enamel. Sometimes the teeth take on a brown stain and look corroded. The disfigurement is permanent, although dentists are now able to remove the stain. Hypoplasia of the enamel and dentin may be seen microscopically. There is a failure in the development of the cementing interprismatic substance of

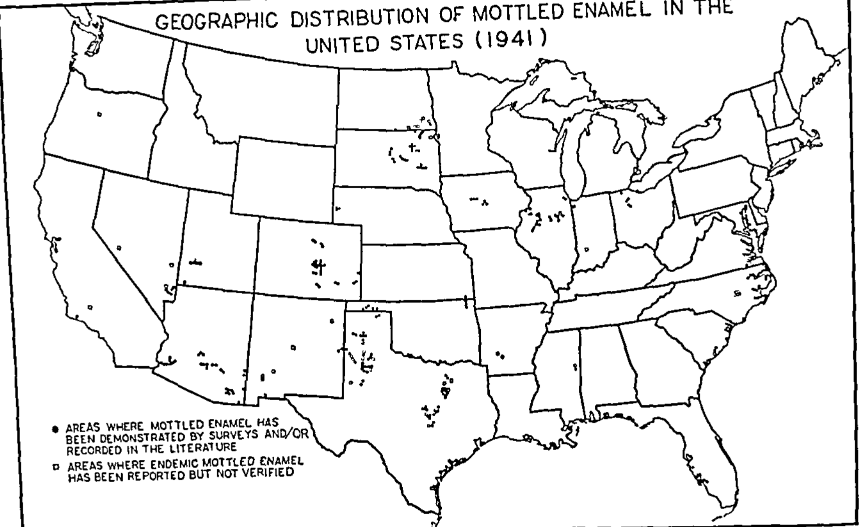


FIG 17 —From H T Dean Fluorine and Dental Health Publication No 19 American Association … of Science Washington 1942 p 9

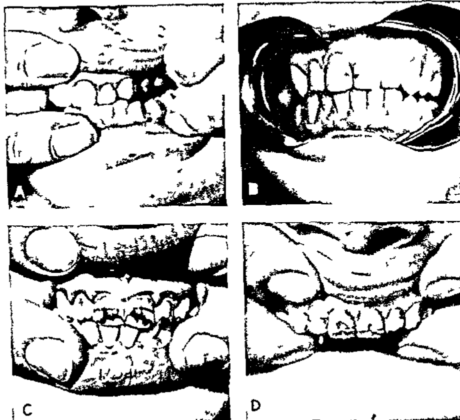


Fig 18 —Endemic dental fluorosis (A and B from Dean McKay and Elvove Pub Health Reports 53 1736 1938, C and D from Fluorine and Dental Health [60]

AMOUNT OF DENTAL CARIES (PERMANENT TEETH) OBSERVED IN 7257 SELECTED 12 14 YEAR OLD WHITE SCHOOL CHILDREN OF 21 CITIES OF 4 STATES CLASSIFIED ACCORDING TO THE FLUORIDE CONCENTRATION OF THE PUBLIC WATER SUPPLY

NUMBER OF CITIES STUDIED	NUMBER OF CHILDREN EXAMINED	NUMBER OF PERMANENT TEETH SHOWING DENTAL CARIES EXPERIENCE* PER 100 CHILDREN EXAMINED (0 100 200 300 400 500 600 700)	FLUORIDE (F) CONCENTRATION OF PUBLIC WATER SUPPLY IN P P M
11	3867		< 0 5
3	1140		0 5 TO 0 9
4	1403		1 0 TO 1 4
3	847		> 1 4

* DENTAL CARIES EXPERIENCE IS COMPUTED BY TOTALING THE NUMBER OF FILLED TEETH (PAST DENTAL CARIES), THE NUMBER OF TEETH WITH UNTREATED DENTAL CARIES, THE NUMBER OF TEETH INDICATED FOR EXTRACTION AND THE NUMBER OF TEETH MISSING (PRESUMABLY BECAUSE OF DENTAL CARIES)

Fig 19 —Amount of dental caries (permanent teeth) observed in 7,257 selected twelve to fourteen year old white school children of 21 cities of 4 states classified according to the fluoride concentration of the public water supply [72]

the enamel with incomplete calcification of the enamel rods and of the dentin. Pitting is caused by a breaking off of the end of the enamel prisms.[80]

2. Relationship between Fluorine and Dental Caries. That the presence of fluorine in the diet decreases the incidence of dental caries is indicated by three types of evidence. In the first place, survey studies have demonstrated that the number of carious teeth per person is greater in communities which have a low-fluorine water supply than in those where the fluorine content is above 1 part per million[81] (Fig. 19). Furthermore, in those cities where the water supply has been changed to reduce the fluorine content from toxic to nearly fluorine-free levels, the incidence of caries is appreciably greater among children born since the water supply was changed than in those who had been exposed to the high fluorine intake.[8] Secondly, in animal experiments rats have been found to develop less caries on a caries-producing diet when fluorine is added to their ration. Thirdly, the incidence of dental caries, particularly among children, has been shown to decrease after cities with a low fluorine water supply have artificially increased the fluoride content to approximately 1 part per million. Carefully conducted surveys before and after fluoridization have been made in Grand Rapids, Michigan, Newburgh, New York, Evanston, Illinois, Brantford, Ontario, and Sheboygan, Wisconsin (Table 21).[75,76c,83] The results in these cities have been so encouraging that as of May 2, 1956, there

TABLE 21.—FLUORIDATION STUDY PROJECTS

Community	*Fluoridation* Date started	*Fluoridation* Report period (years)	Age group (years)	Reduction in decay (per cent)
Grand Rapids, Michigan	Jan., 1945	8	6	70.8
			7	52.5
			8	49.2
			9	48.1
			13	39.7
Brantford, Ont., Canada	June, 1945	7	6	59.4
			7	69.5
			8	51.5
			9	46.2
			13	32.9
Newburgh, New York	May, 1945	7	6	69.4
			7	67.8
			8	40.4
			9	51.4
Evanston, Illinois	Feb., 1947	4	6	73.6
			7	56.4
			8	35.4
Sheboygan, Wisconsin	Feb., 1946	6	9–10 (4th grade)	35.3
			12–14 (8th grade)	29.7

Taken from "The Problem of Providing Optimum Fluoride Intake for Prevention of Dental Caries."[75b]

were 25,900,000 residents of 1293 communities served by 680 separate water supplies which have been fluoridated [84] In other words, about 1 out of every 4 people using central water supplies were drinking water with an adjusted fluoride content In every instance where careful studies have been made there has been a distinct decrease in carious teeth among children As was to be expected, a concentration of 1 part fluorine per million has not led to mottling of the enamel, no other toxic manifestations have been observed In Grand Rapids 0 24 per cent of children showed mottled enamel in a very mild form at the beginning of the fluoridation program in 1944 ten years later the incidence was 0 36 per cent In all instances the mottling is mild not objectionable from either an aesthetic or cosmetic standpoint [83]

The mechanism by which fluorine inhibits the development of caries is not known It was at first though that sound enamel from sound teeth contains more fluorine than that from carious teeth but more recent work has failed to reveal such a difference [85] The external enamel of erupted teeth has a fluoride concentration 6 to 10 times greater than that of the remaining deeper enamel at least a portion of this difference takes place before teeth erupt Fluorine may possibly work by reducing the solubility of enamel in the acids associated with the caries process or by inhibiting bacterial action on food particles and on the tooth The cariostatic effect of fluoride may be exerted in the adult as well as in children [86] Enthusiasm over the fluoride story however, should not blind one to the fact that other nutritional factors besides fluoride are of importance in protecting teeth from caries

Of related interest is the significant observation that the addition of approximately 40 p p m of fluorine to the diet of rats during pregnancy and lactation decreased caries in the offspring Furthermore epidemiological evidence indicates that dental caries may be reduced in children not directly exposed to fluoride themselves but born of mothers who had for a long period of time been consuming drinking water containing excessive amounts of fluorine (14 p p m)[81]

Use of tablets mouthwashes and dentifrices containing fluorine has been warned against but carefully controlled observations are currently being made on the effect of topically applied solutions of fluoride on the caries rate A 2 per cent aqueous solution of sodium fluoride is employed, usually 4 to 8 applications are made In children the incidence of caries is roughly about 25 per cent lower in treated than in untreated teeth Furthermore, in one study which included permanent teeth carious to begin with the number of additional surfaces which became carious was fewer in the fluoride treated teeth by factors of 12 4, 25 2 and 33 1 per cent during each of the first three years respectively In another study application repeated at three year intervals until the children had reached maturity resulted in a caries-rate reduction of about 40 per cent [87] The procedure is probably much less effective when applied to the teeth of adults Much work remains to be done before final evaluation of the technic can be made or the most effective method of application be defined

B Sources and Metabolism of Fluorine —Fluorine is widely distributed in nature particularly in areas rich in phosphates aluminum and volcanic

ash Water becomes contaminated with the element largely when it passes through rich mineral deposits A liter of water with one part fluorine per million contains 1 mg of the element That a significant amount may be obtained from foods, however, is indicated by the fact that natives of a South Atlantic Island have a high incidence of mottled enamel even though their drinking water has only 0 2 part of fluorine per million [88] Their diets contain a large amount of fish (7 p p m), potatoes (1 p p m) and tea (approximately 1 p p m) Average "Toronto, Canada" meals have been estimated to provide from 0 18 to 0 30 mg fluorine per day Baby foods to which bone meal is added may have 13 or 14 p p m Cow s milk is a rather poor source and seems not to be influenced significantly by a high content of fluorine in the drinking water The wide variation in the amount of fluorine in foods is indicated by the fact that seafoods range from 4 2 p p m for canned salmon to 27 p p m for fresh mackerel, peas vary from 0 6 to 6 69 p p m , and fresh fruits range from 0 02 to 0 7 p p m [89] With drinking water containing 1 p p m , it has been estimated that one to three year old children consume 0 4 to 0 8 mg per day, these amounts are under 0 1 mg per kilogram body weight For adults, the quantity of water drunk per day is a major determinant of total fluoride intake, with 1 p p m in drinking water, the average ingested daily in water and food varies from about 0 5 to 4 mg

Information about the metabolism or precise function of fluorine is extremely meager Fluorine deficiency has never been produced experimentally, the element's right to be called an essential nutrient is dependent solely on the development of dental caries when intake is low Absorption depends in large part on the solubility of the fluorine containing salt or material No measurable retention occurs on an intake of 0 6 mg per day, but at higher levels retention probably occurs throughout life [90] In rats, retention is increased when the fat content of the diet is increased from 5 to 20 per cent [91] Elimination occurs largely through the urine Urinary excretion increases as the content of fluorine in drinking water increases, sweat and perhaps insensible perspiration also account for an appreciable loss of fluorine from the body One third to one half of the fluoride absorbed into body fluids is rapidly deposited in the skeleton as fluorapatite [75b] Blood fluoride levels have been estimated to be about 10 to 40 micrograms per ml Fluoride once deposited in the skeleton is by no means permanently fixed and may be mobilized—a safety mechanism tending to maintain the total amount of fluoride in the body at a low level From animal studies it appears there is a safety factor of approximately 50 fold between the amounts of fluoride necessary to produce skeletal changes of fluorosis and that which would be retained at drinking water levels of 1 p p m

C **Evidences of Fluorine Toxicity**—In addition to chronic dental fluorosis, fluorine has been reported to cause certain skeletal abnormalities Lesions resembling osteosclerosis have been reported in areas where inhabitants are exposed to large concentrations of fluorine (20 to 80 mg or more per day) for long periods of time [75b, 92] A detailed medical and laboratory study made on adults living in Bartlett, Texas, where the drinking water contains 8 p p m fluoride failed to reveal any abnormalities other than dental fluorosis [93] The subjects were examined in 1943 and again

in 1953, the average length of fluoride exposure was 36.7 years. Subjects were compared with a group of people in a neighboring town where the fluoride content of drinking water was only 0.4 p.p.m.

In India impaired renal function has been described in patients with a severe form of osteosclerotic change attributed to fluorine.[94] However, urinary findings in men living in the fluoride areas of the West Texas Panhandle where the fluorine content of drinking water may be as high as 5–6 p.p.m. do not differ from the normal.[65]

Cattle consuming as high as 1.0 mg. of fluorine per kilogram body weight per day over periods of five to ten years show no detectable effects except slight mottling and wear on the incisor teeth. With 2.0 mg. per kilogram of body weight per day, however, there is severe damage to teeth and bones, lameness, stiffness, and emaciation.[95] Fluorine toxicosis occurs in the dairy cow when the fluorine content of compact and of cancellous bone is in excess of 5,500 and 7,000 p.p.m., respectively; on a normal ration by contrast the content is less than 1,000 p.p.m. At the higher levels exostoses were found, particularly in metacarpal and metatarsal bones.[96]

Because fluorine is widely used in industry, insecticides, and sprays, acute poisoning is not unusual.[9] The fatal oral dosage is approximately 0.5 mg. per kilogram of body weight. The following manifestations appear: salivation, nausea, vomiting, muscular weakness, excitement, and tremors and convulsions. The blood pressure falls because of central vasomotor depression and a direct toxic effect on the myocardium. After an initial acceleration and deepening of respiration, respiration is depressed and death occurs.

MANGANESE

Evidence that manganese is an essential trace element for animals is threefold: (1) it is required for the activation of certain enzymes (*i.e.*, arginase, leucine aminopeptidase, bone phosphatase, and enzymes active in oxidative phosphorylation) and may be a part of the prosthetic group of liver arginase;[1, 97–100] (2) manganese deficiency has been produced experimentally in a number of animal species;[1, 101, 102] and (3) manganese deficiency is related to the naturally occurring disorders of poultry known as 'perosis' and nutritional chondrodystrophy. The principal manifestations of induced deficiency are poor growth, decline in reproductive capacity, faulty bone growth, and nervous disorders. The essentiality of manganese for man has never been clearly demonstrated, but there is every reason to believe that the functions of the element are the same as in other mammals. More complete coverage of the subject is provided by the fine reviews of Oettingen,[103] Underwood,[1] and Cotzias.[102]

Metabolism, Requirement, and Sources of Manganese.—Manganese, like iron, is rather poorly absorbed from the intestinal tract. High dietary concentrations of calcium and phosphorus decrease absorption, but information about the factors that control assimilation or about uptake from foods is meager. It presumably is transported in plasma, even though the blood concentration is low—2.4 ± 0.8 micrograms per 100 ml. distributed approximately equally between cells and plasma.[104] The total body manganese in the human has been estimated to be only 10 to 20 mg.,[105] but concentra-

tions given for individual tissues would add up to more than that figure in many cases 3 5 mg per kilogram of wet weight for bone, 2 0 to 2 5 mg per kilogram for the liver, pituitary and pineal body, 0 7 to 1 7 mg per kilogram for the intestinal tract, pancreas, kidney, and salivary gland [105] The concentrations in individual organs tend to be similar in different species and to remain relatively constant throughout the life of an animal [1, 10] Within cells manganese is located both in the nucleus and in cytoplasmic organelles, the turnover rate in mitochondria is particularly high [105, 106] Manganese is excreted largely via the intestinal tract with at least some of the excreted metal reaching the duodenum in bile and pancreatic juice, urinary losses are very small

Estimates of minimal requirements for dietary manganese are difficult to obtain from the literature, even for experimental animals, because they usually are stated in terms of mg per kilogram of diet, they vary with the type of diet (particularly Ca and P content), and because different amounts are required for the promotion of maximum growth, optimal bone development etc [1, 101, 105] Some workers believe that the requirements are higher for birds than for mammals It has been estimated that the diet of a normal human contains from 3 to 9 mg per day [107, 108] and that children may require as much as 200 micrograms per kilogram of body weight [109] Plant foodstuffs are the chief source of manganese in the diet Tea, coffee, blueberries, the bran of cereals, dry legume seeds, and nuts are particularly rich sources Non leafy vegetables, animal tissues, poultry and poultry products dairy products fish, and sea foods are relatively poor sources (0 25 to 1 5 parts per million in fresh edible portion) [1] While milk contains only small amounts, the transfer of radioactive manganese from the mother to the tissues of nursing rats has been traced

Manifestations of Manganese Deficiency [1, 101, 105]—When mice and rats are reared on a manganese deficient diet, decreased growth bone changes (decreased length breaking strength and density) testicular atrophy and abnormalities of reproductive function in the females are produced Liver arginase bone phosphatase, and blood phosphatase activities are all reduced Manganese deficient pigs show similar changes together with skeletal or muscular weakness, increased back fat thickness, and poor udder development with almost complete absence of milk production Deficient cows are slower to exhibit oestrus, slower to conceive, and tend to produce calves with weak legs The ovaries in these animals contain only 0 85 rather than 2 parts per million of manganese while the liver and other tissues showed no difference from the normal Manganese is needed along with choline and biotin to prevent a disease in fowl called perosis Perosis is characterized by an enlargement of the tibial-metatarsal joint, twisting and bending of the distal end of the tibia and of the proximal end of the metatarsus, and slipping of the gastrocnemius tendon from its condyle A lowering of bone and blood phosphatase activity precedes the appearance of perosis Eggs produced by manganese-deficient hens hatch very poorly when the embryos do grow, they show chondrodystrophic changes greatly shortened and thickened legs and shortened wings disporportionate shortening of the lower mandible (parrot beak, anterior bulging of the skull, edema above the atlas joint of the neck, protruding abdomen (appar-

ently due to a relatively large amount of unassimilated yolk), retarded down and body growth. In addition to perosis and chondrodystrophy, deficient chicks frequently demonstrate nervous symptoms, particularly ataxia. The high requirement of birds for manganese is interesting since their tissues have no arginase. Manganese deficiency in man has not been recognized.

Toxicity of Manganese.—Workers exposed to manganese dust (miners, ore crushers, sieve operators) may absorb enough of the metal through their respiratory tracts to develop toxic manifestations.[1, 107, 108] Clinical changes come on insidiously with asthenia, anorexia, apathy, headache, impotence, leg cramps, and speech disturbances. Eventually the syndrome simulates a progressive hepatolenticular degeneration and in some respects resembles Parkinson's disease. The facial expression is mask-like, the voice monotonous. An intention tremor, muscular rigidity, and a spastic gait appear. Tendon reflexes are exaggerated and patellar clonus may be found. Pulmonary changes similar to pneumoconiosis may occur. Mild cases removed from further exposure may recover. With more severe toxicity the disease may remain stationary or progress; treatment has been unsatisfactory, although there is now one report of response to EDTA (ethylenediaminetetraacetate, dicalcium, disodium).[110]

SELENIUM

Selenium has recently been recognized to be an integral part of Factor 3, a dietary agent which prevents dietary liver necrosis in the rat, multiple necrotic degeneration of the heart, liver, muscle, and kidney in the mouse, and a fatal exudative diathesis in certain fowl.[111, 112] On this basis, it may probably be regarded as an essential trace element. The above diseases result from a multiple deficiency produced by diets deficient in vitamin E and Factor 3, but each of these substances protects by itself. It is claimed that the effectiveness of L-cystine in protecting against dietary liver necrosis is the result of contamination with traces of a Factor 3—active selenium compound.[113] While selenium is present in a bound form as an organic compound, Factor 3 may be replaced at slightly higher levels in the diet by sodium selenite, selenium amino acids, and several other selenium compounds.[114] Sodium selenite is 500 times more effective in offering protection than is vitamin E. The site of action and the chemical nature of the metabolically active form are not known, but may be in the respiratory enzyme systems of the cell.

Until the above observations were made, interest in selenium centered chiefly about its toxic effects in producing alkali disease and blind staggers in livestock, particularly in the Great Plains states of this country.[1]

ZINC

The evidence which establishes zinc as an essential trace element is two-fold: zinc deprivation in animals has produced deficiency disease, corrected by replacement of the element, and zinc-containing enzymes have been isolated from animal tissues.[115–117] One of these enzymes, carbonic

anhydrase, catalyzes the reaction $CO_2 + H_2O \leftrightarrows H_2CO_3$, and is as important to carbon dioxide transport as hemoglobin is to oxygen transport Zinc deficiency in man has not been recognized, but changes in the blood zinc level produced by disease have been extensively studied

Metabolism, Requirements, and Function—The adult human body contains about 2 grams of zinc, an amount considerably larger than that of the other trace elements except iron Tissue concentrations vary from 10 to 200 micrograms per gram of wet weight Most organs, including the pancreas, contain from 20 to 30 *micrograms per gram*, the liver, voluntary muscle, and bone have 60 to 180 micrograms per gram Large quantities have been found in the corneal epithelium, the iris, retina, and lens The prostate, prostatic secretions, and spermatazoa are also remarkably high in their zinc content

The normal human daily intake of zinc is 10 to 15 mg How much of this is absorbed, is not known Excretion occurs largely through the gastrointestinal tract Human whole blood contains about 900 micrograms of zinc per 100 ml, an average of 120 micrograms per 100 ml is in the plasma Roughly 34 per cent of the plasma zinc is firmly bound to a globulin, the remaining 66 per cent is more loosely bound to a plasma protein and probably represents the transport fraction All or most of the zinc in red cells is in carbonic anhydrase—the only carbonic anhydrase found in blood Leucocytes contain 3 per cent of the total zinc in blood, 0 032 microgram per million cells, in a concentration per cell approximately 25 times that of the erythrocytes, 80 per cent of the white cell zinc is in the form of an apparently specific zinc protein of unknown function Under normal circumstances, blood zinc levels are relatively stable The zinc and carbonic anhydrase content of the red cells of newborn infants, however, is only about 25 per cent of adult values, the level doubles by the end of one year and reaches normal values by the ages of 10 to 12

When radioactive zinc is injected, it disappears rapidly from the plasma and is initially concentrated in the liver, which at the end of several hours contains almost 40 per cent of the injected dose There is also a considerable accumulation in the pancreas, kidneys, and pituitary The isotope concentration gradually falls in these organs, slowly rises in erythrocytes and bone, radioactivity in tissues can be detected for as long as 8 months to a year Zinc has been shown to pass the placenta Feces contain about 10 mg and urine about 0 4 mg per day, a portion of injected radioactive zinc is eliminated in the external pancreatic secretions and in the duodenal juice but only in small amounts by the bile

Some of the functions of zinc have been identified by a study of known zinc enzymes *Carbonic anhydrase* (0 33 to 0 34 per cent zinc) makes possible the rapid elimination of carbon dioxide and is of great importance in carbon dioxide transport It is present in many tissues other than erythrocytes *Carboxypeptidase*, found in bovine pancreatic juice, contains one atom of zinc per molecule of protein, splits terminal amino acids from peptides having a free alpha carbon group adjacent to the peptide bond, and is implicated in proteolysis within the intestinal tract

Four zinc-containing *dehydrogenases* have been identified, all four are dependent for their activity on diphosphopyridine nucleotide (DPN)

Alcohol dehydrogenase of horse liver oxidizes vitamin A and reduces retinene, it may be identical with retinene reductase

There is no convincing evidence that zinc is essential to the formation or action of insulin. No significant difference in the zinc content of the pancreas in normal persons and diabetic patients has been detected. Some of the zinc in pancreas can be accounted for by carboxypeptidase. Zinc blood levels of diabetic patients are normal. The relation of the element to the activation of other hormones is not clear. It has been reported to augment the action of the follicle stimulating and luteinizing hormones of the anterior pituitary when tested on hypophysectomized rats, and to prolong the water retaining action of pituitrin in frogs

Zinc Deficiency in Animals —Rats and mice fed a diet containing 1.6 p p m or less of zinc gain weight poorly and develop alopecia about the neck and shoulders which sometimes spreads and involves the whole ventral surface of the body. Zinc deficient animals show extreme parakeratosis with a thick layer of partially keratinized cells in the esophagus. There is hyperkeratinization of the skin, thickening of the epidermis and loss of hair follicles with persistence of sebaceous glands. In an occasional animal vascularization of the cornea with leukocytic infiltration has been observed. Carbonic anhydrase activity is not decreased in zinc-deficient rats and there seems to be no disturbance of carbohydrate metabolism although the absorption of glucose is apparently impaired

A disease resembling parakeratosis has been produced in hogs fed a diet with a relatively low zinc content and supplemented with calcium phosphate[16]. The animals developed a severe dermatitis frequently accompanied by diarrhea, vomiting, anorexia, weight loss and even death. These manifestations occured only when calcium phosphate was added for reasons that are not clear, the absorption of zinc may possibly have been blocked

Changes in Blood and Urine Zinc Content with Disease —Extensive studies of the blood and urine zinc in disease have revealed a number of interesting and puzzling changes, few of which are understood[16,17]

1 *Plasma Zinc* —Lower than normal levels of plasma zinc have been found in certain infections, myocardial infarction and untreated pernicious anemia. Within 24 hours after vitamin B_{12} is given to patients with pernicious anemia a rise in the plasma zinc is observed with a return to normal values at about the time of the reticulocyte peak. All of the changes are apparently due to a decrease in the loosely bound fraction. No diseases characterized by higher than normal levels have been recognized

2 *Erythrocyte Zinc* —In normal individuals, patients with polycythemia and most anemias, the erythrocyte zinc (and carbonic anhydrase activity) varies with the hematocrit. In sickle cell anemia and in untreated pernicious anemia, however, the values are elevated. In pernicious anemia the elevation is corrected by vitamin B_{12} therapy. High levels are also found in the erythrocytes of patients with acute intermittent porphyria

In newborn infants the red cell zinc is only 25 per cent of normal and even lower in premature babies

3 *Leukocyte Zinc* —The zinc in leukocytes of patients with acute lymphocytic leukemia, chronic lymphocytic leukemia and chronic myelocytic leukemia may be reduced to only 10 per cent of normal values

These low levels are corrected when a remission is induced by appropriate therapy, but are not altered by the intravenous administration of zinc In patients with refractory or hypoplastic anemia, the white blood cell zinc may be elevated even though a leukopenia exists

4 *Zincuria* —Patients with proteinuria may excrete as much as 2 1 mg of zinc in their urine per day (normal 0 3 to 0 4 mg)

5 *Acute intermittent porphyria* is accompanied by the excretion of a zinc uroporphyrin complex, present also in the liver A zinc coproporphyrin complex has also been identified in the urine of patients with acute lead poisoning and acute rheumatic fever

6 *Zinc and Postalcoholic Cirrhosis* —The identification of zinc-containing dehydrogenases in the livers of certain animals has prompted a study of the zinc content of the blood and livers of patients with hepatic cirrhosis Serum concentrations are reduced, particularly in hepatic coma where values less than 30 micrograms per 100 ml have been found Urinary excretion is increased and, in patients who die of the disease there is significant reduction in the concentration in the liver

Toxicity of Zinc —In experimental animals the feeding of excess dietary zinc has been reported to produce hypochromic anemia, subnormal growth and reproductive failure [119] The metal was found to have two separate effects on rats one upon the hemoglobin level, and the other upon the growth rate Cats fed large doses of zinc will occasionally develop fibrosis of the pancreas [118]

The amounts of zinc present in food or water are not sufficient to cause toxic symptoms However, enough zinc may apparently be dissolved from cooking utensils made of galvanized iron to cause poisoning if the food is acid in reaction It is reported that a group of soldiers were accidentally poisoned by drinking limeade prepared in a galvanized can [120] Nausea, vomiting, diarrhea, and abdominal pain are common symptoms The inhalation of zinc dust results in a syndrome called "metal fume fever" in which chills, fever, and a marked leukocytosis occur Zinc seems to exert its toxic action by precipitating the protein of the gastrointestinal mucosa or the bronchial epithelium

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Chapter 10—(*Continued*)

B. Iodine

By Monte A. Greer

It is only within the last twenty-five years that iodine has become universally recognized as an essential dietary factor. Although both seaweed and burnt sea sponge had been recognized for centuries in both Europe and Asia as an effective treatment for goiter, it was not until 1811 that Courtois discovered iodine while attempting to extract saltpeter from seaweed vats for Napoleon's army. Shortly thereafter, Coindet, a Geneva physician, deduced that this new element might be the active principle in both seaweed and sponge. The remarkable regressions he obtained with iodine in simple goiter were reported in 1820.[10] Confirmation quickly came from diverse parts of the world, and this therapy rapidly became established. Indeed it was said that among the people of Lausanne, "The tincture of iodine bottle replaced the bonbonniere" and that no one would think of paying a social visit without taking his dropping bottle with him.

In 1831, Boussingault suggested that the goitrous inhabitants of Colombia might well benefit from iodinization of their salt supply.[5] Prevost and Maffoni are generally credited, however, with being the first to suggest, in 1846, that iodine deficiency was actually the cause of goiter.[35] It was the French chemist, Chatin, who began a systematic investigation of the iodine content of soil, air, and water. His results appeared in a series of papers between 1850 and 1896[6-8] and led him to the conclusion that there was no question but that goiter almost invariably was associated with a deficiency of environmental iodine. Although some investigators agreed with Chatin's views, there were many who questioned the accuracy of his methods and seriously doubted that iodine deficiency had any connection with the development of goiter. Owing to this difference of opinion and to the fact that certain people with simple goiter who were given large amounts of iodine therapeutically developed thyrotoxicosis or "Jod Basedow,"[11] the French Academy of Sciences appointed a committee to judge the relative merits of the iodine deficiency theory. Because some of Chatin's results showed that there was a high iodine content associated with areas in which goiter was common and because of other reasons, the Commission reported unfavorably and the theory subsequently suffered a great loss of favor.[7] Indeed many scientists disputed whether iodine ever reached the thyroid gland.

Interest was reawakened in 1895 when Baumann[4] discovered that iodine was present in the thyroid gland and was contained there in organic binding. Shortly after this, many people began repeating Chatin's experiments in various parts of the world.[33] Among the most active investigators were McClendon in the United States, Von Fellenberg in Switzerland, Hercus in New Zealand and Orr in Great Britain.

David Marine, of the United States, deserves considerable credit for stimulating this renewed interest in iodine. Especially significant was his therapeutic trial with Kimball, in the schools of Akron, Ohio in 1917 and 1918.[30] It was found that small doses of iodine given over a ten-day period twice a year would greatly reduce the incidence of simple goiter in the children of that area. Similar results showing the remarkable reduction in the incidence of goiter following prophylaxis with iodinated salt soon became commonplace.

THE METABOLISM OF IODINE

The human thyroid gland in its normal state contains between 8 and 10 mg of iodine. Since the average gland weighs between 20 and 25 gm., this means that there is between 0.4 and 0.5 per cent iodine in the gland. Assuming that almost all the iodine secreted by the thyroid is in the form of thyroxin, the average daily output of thyroxin is about 100 micrograms of thyroxin iodine per day.

The normal iodine requirements for man have been estimated on the basis of urinary and fecal excretion studies to be between 100 and 200 micrograms per day under ordinary physiological circumstances. It has been estimated from the average content of iodine of various foodstuffs in the diet of a normal English city dweller that the intake would be slightly below normal daily requirements.[27]

The iodine content of most foods from the sea is much higher than that of other forms. It is especially high in seaweed, shellfish, and haddock. Most terrestrial foods have approximately the same iodine content, although that of the plant foods can be greatly increased by adding iodine-rich minerals to the soil in which they grow. Spinach has a much higher proportion of iodine than any other vegetable.

The amount of iodine added to salt varies from country to country. In some places like Italy and Switzerland where there is great fear that excessive iodine may induce hyperthyroidism in people with large non-toxic goiters, the amount added may be so small that little prophylaxis is accomplished. Assuming a daily intake of salt of approximately 10 gm. per day, a person in the United States receiving iodized salt would have a daily intake of 1 mg. of iodine per day. In Switzerland or Italy the daily intake would be only 100 micrograms per day, excluding other dietary sources of iodine. This may explain why the results of iodine prophylaxis of simple goiter have been somewhat more dramatic in the United States than in certain other countries.

Most of the iodine present in the body is supplied by the ingestion of foodstuffs and, to a lesser extent, water. A small amount may also be taken in by absorption through inspired air in regions along the seacoast where there is relatively high iodine saturation, but the amount thus absorbed is so slight as to play an insignificant role in the metabolism of iodine as a whole.

Once ingested, iodine is absorbed chiefly from the small intestine. It then circulates as both inorganic iodide and organic iodine, but it apparently only enters the thyroid gland as the iodide ion. There is a mechanism for

TABLE 22 — AVERAGE IODINE CONTENT OF SOME EVERYDAY FOODS[27]

	Iodine content µg/kg Fresh basis	Iodine content µg/kg Dry basis
Milk and Milk Products		
Milk (cow's)	35	
Cheese	51	
Butter	56	
Mean	47	
Eggs		
Hen's eggs	93	
Mean	93	
Meat and Meat Products		
Mutton	27	
Beef	28	
Veal	28	
Pork	45	
Bacon	77	
Lard	97	
Mean	50	
Fish (a) Marine Fish		
Sole	163	1072
Sea bass	250	471
Sardines	284	745
Mackerel	371	1031
Halibut	520	2225
Herring	520	1358
Sea perch	742	3105
Cod	1463	7493
Haddock	3180	15941
Mean	832	3715
(b) Anadromous Fish		
Sea trout	320	1028
Salmon	341	1030
Mean	330	1029
(c) Freshwater Fish		
Carp	17	68
River bass	30	115
Lake trout	31	88
River perch	40	194
Mean	30	116
Fish Oils		
Salmon oil	2450	
Cod liver oil	8387	
All others taken together	3052	
Mean	4630	

	Iodine content µg/kg Fresh basis	Iodine content µg/kg Dry basis
Shellfish		
Crab and crabmeat	308	1292
Oysters	577	4712
Clams	783	3595
Lobster	1020	4744
Shrimps	1300	4987
Mean	798	3866
Cereal Grains and Products		
Rice	22	39
Maize	27	43
Wheat	37	44
Flour	42	
Bread	58	
Barley	58	92
Oats	60	91
Rye	72	84
Mean	47	65
Vegetables		
Mangolds	11	192
Gourds, pumpkins, marrow	12	600
Cauliflower	12	221
Beetroot	21	233
Onions	22	204
Cucumber	25	400
Lettuce	26	668
Carrots	38	202
Turnips	40	343
Asparagus	42	1102
Potatoes	45	197
Cabbage	52	260
Spinach (excluded from mean)	201	1636
Mean	29	385
Legumes		
Peas	23	223
Beans	36	245
Mean	30	234
Fruits		
Pears	10	62
Tomatoes	17	196
Apples	16	277
Cranberries	29	100
Mean	18	159

selectively concentrating iodine by the thyroid gland, and the concentration of iodide in the thyroid to that in the blood is designated as the thyroid serum iodide ratio. This ratio varies with different species, but for man, as for most other animals, it is approximately 25:1. This ratio can be greatly increased in hyperthyroidism or decreased in hypopituitarism.

TABLE 23.—AVERAGE IODINE CONTENT OF SOME ANIMAL FEEDINGSTUFFS[28]

	Iodine content µg/kg			*Iodine content µg/kg*	
	Fresh basis	*Dry basis*		*Fresh basis*	*Dry basis*
Fresh Green Fodder			*Straw*		
Alfalfa	28	313	Wheat straw		419
Mixed pasture	60	553	Oat straw		468
			Rye straw		490
Mean	44	433	Barley straw		630
Hay			Mean		502
Timothy hay	80	262	*Oilseed Meals*		
Alfalfa hay	188	274			
Sweet clover hay		320	Linseed cake meal		110
Meadow hay	194	368	Cottonseed meal		149
Oat hay	219		Soyabean meal		170
Soyabean hay	225	526	Groundnut cake meal		200
Mean	181	350	Mean		157

TABLE 24.—AVERAGE DIET OF ENGLISH CITY DWELLER[41]

	Weekly consumption per head		*Iodine µg/kg fresh basis*		*Weekly iodine intake per head (µg)*
Milk	4.8 pts	@	35	=	95
Cheese	2.2 oz	@	51	=	3
Meats	22.7 oz	@	50	=	32
Fish	8.4 oz	@	832	=	198
Eggs	2.9 eggs	@	93	=	12
Fats	10.7 oz	@	56	=	17
Fruit	22.4 oz	@	18	=	11
Vegetables	99.9 oz	@	29	=	82
Cereals	85.4 oz	@	47	=	113
Sugar	10.9 oz	@	Nil	=	Nil
Preserves	6.2 oz	@	12	=	2

Iodine intake per week = 565 µg

The iodide compartment in the thyroid seems to be freely exchangeable with that of the blood and other extracellular spaces of the body. Iodide is also concentrated by the salivary glands, by the gastro-intestinal tract and by the hair follicles.[31] Nearly 100 per cent of the ingested iodide,

however, either goes into the thyroid gland or is excreted in the urine by the end of twenty-four to forty-eight hours In the normal thyroid, once the iodide has been concentrated, it is quickly oxidized and is then bound to protein in the colloid, forming monoiodotyrosine, diodotyrosine, thyroxin, diiodothyronine and triiodothyronine These compounds are contained in the complex known as thyroglobulin So far as can be determined from current techniques of autoradiography, the iodide ion is not concentrated in the cell but in the colloid

Much more thyroid hormone is contained in the colloid than is required for daily use Proteolytic enzymes are believed to break down the thyroglobulin into iodinated amino acids, and apparently some deiodination of these amino acids occurs in the thyroid gland also Only thyroxin and a small amount of triiodothyronine are actually removed from the colloid and secreted by the thyroid into the blood stream Leblond has compared the formation of thyroid hormone in the colloid and its enzymatic release and secretion into the blood stream to processes occurring in the gut, from which the thyroid is derived The thryoglobulin formed in the colloid is analogous to the enzymes secreted into the lumen of the gut The digestion of thyroglobulin and the absorption and secretion of thyroxin and triiodothyronine are equivalent to proteolysis and absorption of amino acids from the gut

Thyroxin is the main constituent of thyroid hormone in the blood and is bound loosely to an inter-alpha globulin known as "thyroxin binding protein" (TBP) [39] There is recent evidence that a pre-albumin fraction of the serum proteins also binds a significant amount of thyroxin [25] Triiodothyronine is 3 to 4 times as active physiologically as thyroxin [4] There has been some suggestion that because of triiodothyronine's greater activity and because it has a higher intracellular concentration in most tissues than thyroxin that it is the active thyroid hormone Presumably it is formed by deiodination of thyroxin at the cellular level However, there is considerable doubt that triiodothyronine is really the active thyroid hormone Other metabolic degradation products, such as thyroxamine, Tetrac and Triac (the acetic acid analogues of thyroxin and triiodothyronine, respectively) have also been proposed as the intracellulary active thyroid hormone A final answer to this problem must await more definitive future investigations

The breakdown of thyroid hormone in the peripheral tissues occurs at a relatively slow rate It has been estimated that the half-life of the hormone, once it has been secreted from the thyroid gland, is approximately six to eight days [37] About 40 per cent is excreted in the urine as iodide, while about 10 per cent is excreted in the feces in a protein-precipitable form There is an important entero-hepatic circulation of thyroxin in the body [1] Thyroxin is conjugated to glucuronic acid and secreted in the bile, where, presumably, the glucuronide is hydrolyzed by the glucuronidase of the bacterial flora of the intestine and the released free thyroxin is reabsorbed into the blood Although large amounts are excreted through the bile in this way, most of it must be reabsorbed The enterohepatic cycle does not appear to be so important in man

THE CONTROL OF IODINE METABOLISM

Since the pioneer work of P E Smith[40,41] and Bennett Allen, it has been known that the pituitary gland is of prime importance in maintaining the metabolism and size of the thyroid gland There is a reciprocal relationship between the circulating levels of pituitary thyrotrophin and of thyroid hormone The pituitary acts as a thermostat and the thyroid as a furnace The hypophysis secretes thyrotrophin which stimulates the growth and metabolism of the thyroid The thyroid gland is thus incited to secrete thyroxin which not only accelerates peripheral metabolism but also acts on the pituitary to inhibit the further secretion of thyrotrophin A finely adjusted balance is thus maintained which keeps the circulating level of thyroid hormone at a euthyroid level If the pituitary gland is removed, the thyroid atrophies and very little thyroid hormone is formed On the other hand in patients with myxedema, there is a marked increase in the secretion of thyrotrophin Anything which lowers the level of circulating thyroid hormone, either by increased physiologic demand or by pharmacologic interference with the synthesis of thyroid hormone, will result in an increased secretion of thyrotrophin and a consequent increase in thyroid function and size

There has been recent evidence which indicates that this control of the thyroid is not determined directly by the pituitary, but that the hypothalamus and possibly other parts of the central nervous system play a significant role Destruction of an area in the anterior hypothalamus in the vicinity of the paraventricular nucleus will result in profoundly decreased thyrotrophin secretion by the anterior pituitary [17,19] There appear to be separate receptor sites in the thyrotrophin area of the hypothalamus and in the anterior pituitary which are sensitive to alterations in thyroxin concentration The microinjection of very small, systemically ineffective amounts of thyroxin into both these areas will result in decreased TSH secretion [48]

Iodine itself also exerts a direct effect on the thyroid gland Wolff and Chaikoff[47] found in rats that when the level of iodine in the serum went above 25 micrograms per 100 ml the synthesis of thyroid hormone ceased Subsequently Raben[36] showed that this effect was due to the concentration of iodide within the thyroid gland and not to its concentration in the blood More recently it has been shown that the thyroid serum iodide ratio in hypophysectomized animals injected with small daily doses of thyrotrophin can be markedly changed by altering the iodine intake of the animals [45] Iodide also will inhibit the release of hormone from the thyroid gland in thyrotoxic patients [15,23,4] This inhibitory effect is not produced in euthyroid patients however [3]

Within recent years it has become apparent that there are a number of drugs which are capable of interfering with iodine metabolism by the thyroid These are generally called anti-thyroid drugs and can be divided into two types The first group contains those drugs which inhibit the concentration of iodine from the blood by the thyroid gland and so far as is known to date consists generally of anions Thiocyanate is the representative of this group most likely to be encountered clinically These

drugs have no effect on the binding of iodine to protein but only on the step of concentration of inorganic iodide Thus, if the dietary intake of iodine is sufficient to insure an adequate supply of iodide within the thyroid gland, even though the concentration gradient is destroyed, synthesis of thyroid hormone will proceed normally and deficiency of thyroid hormone will not develop

The second group of compounds consists of thiourea, thiouracil, and related drugs, as well as aniline and resorcinol derivatives These compounds act after iodide concentration and appear to block the oxidation of iodide to elemental iodine and thus the binding to protein Synthesis of the thyroid hormone can thus be effectively prevented even in the maintenance of a more than adequate supply of iodide ion within the thyroid gland

The steroid hormones have also been found to exert an effect on iodine metabolism, but the mechanism of their action has not been completely elucidated Cortisone has been found to depress the uptake of radioactive iodine by the thyroid gland in both experimental animals and man, but it is quite likely that this action on iodine uptake is mediated largely through its renal effect [5] Cortisone enhances renal clearance of iodide, thus increasing the competition of the kidney and thereby decreasing the amount available to the thyroid gland Some workers have found that there is also depression of the protein-bound iodine in patients treated with cortisone, but the significance of this finding is at present obscure Certainly the occurrence of clinical hypothyroidism in patients treated with cortisone must be an extreme rarity

Estrogen also has been found to affect iodine metabolism Patients receiving it in large dosage have been found to have an elevation of their protein-bound iodine which returns to normal levels when treatment is stopped [13] This elevation of protein-bound iodine is due to an increased capacity of the specific thyroxin-binding protein in the blood and is not due to any specific change in thyroidal activity [38]

PHYSIOLOGIC VARIATIONS IN IODINE REQUIREMENT

Changes in the physiologic state conditioned by both endogenous and exogenous factors have long been known to exert a significant influence on thyroid function Since antiquity it has been noted that women frequently develop goiter while pregnant It has also been observed that the occurrence of thyroid enlargement is common during puberty in both boys and girls Presumably during these periods, the demands of the body for thyroid hormone are greater, thus causing an augmented secretion of thyrotrophin and hence an increase in thyroid size and activity When these excessive demands have abated, the thyroid usually returns to its former size During pregnancy there is dually increasing level of the blood protein-bound iodine which ex ormal physiologic range of non pregnant w by the thi [34] These levels return to normal followi As has above, a similar increase in protein-bou n be dupl dministering estrogen to either men or w

Animals in a cold environment will develop enlarged thyroid glands and a columnar thyroid epithelium. Conversely, a hot environment will cause a decrease in thyroid size and a flattening of the thyroid epithelium. Although in laboratory animals these changes unquestionably occur, it is doubtful whether temperature plays much of a part in the regulation of iodine metabolism in man. Goiter is rare among the Eskimos and in Greenland, whereas it is common in Sumatra and Java. Presumably, this lack of effect of temperature in man is due to his ability to adjust to his milieu by either increasing or decreasing the amount of clothing covering his body.

Not infrequently premenopausal women with thyroid enlargement note that their cervical swelling increases in size during the time of their menstrual periods. Presumably, this is also due to an increased demand for thyroid hormone during their courses.

METHODS OF DETERMINING THYROID FUNCTION

Many laboratory procedures are now available for assessing thyroid function. These include in addition to basal metabolic rate determination, the test for radioactive iodine uptake and protein bound iodine determination.

A widely used screening procedure available at the present time involves the use of radioactive iodine. The most common technique is the determination of the amount of an administered dose of radioiodine contained in the thyroid gland at the end of twenty-four hours. The euthyroid range in most clinics is between 15 and 50 per cent. In patients with hypothyroidism the uptake is usually below 10 per cent. For patients with hyperthyroidism it is usually above 50 per cent. As in the case of the basal metabolic rate, there is some overlap between the results obtained in various groups by means of this technique. Some refinements of the use of radioiodine have been proposed which are said to be more specific for determining thyroid function than in the measurement of the twenty-four hour uptake alone; however, these methods are usually more complex and they require a good deal more of the technician's time than does the twenty-four hour uptake determination. For routine screening purposes, the increased accuracy obtained by these refinements is probably not worth the added effort.

The so-called "conversion ratio" has also been used as a relatively simple test of thyroid function by the use of radioactive iodine.[12] This test involves determining the amount of protein bound to free radioiodine in the plasma at the end of a specified period of time, usually forty-eight to seventy-two hours. Although this seems to be about as accurate as the twenty-four hour radioiodine uptake, it requires the use of a much larger tracer dose of radioactive material and hence is probably not as safe as tests employing smaller doses.

Another good method of assessing thyroid function is the determination of the level of hormone circulating in the blood. This is calculated as protein bound iodine and is about as reliable as the twenty-four hour uptake of radioiodine. Normal levels in most laboratories are from 4 to 8 micro-

grams per 100 ml for euthyroid patients The butanol-extractable iodine, or BEI, is preferred by some over the protein-bound iodine determination [3] BEI more accurately measures the thyroxin-like iodine in the blood and thus is not elevated by exogenous iodides as is the PBI Unfortunately, determination of the protein-bound iodine is a much more laborious procedure than utilization of radioactive iodine and *in vivo* counting, therefore, the latter is to be preferred, for reasons of economy, as a routine screening procedure

The cholesterol level in the blood is also of some help in the diagnosis of thyroid disease, but it is much less specific than the other parameters mentioned In some patients with hyperthyroidism, the cholesterol falls below the normal limits of 150 to 250 mg per 100 ml In a greater proportion of patients with myxedema, the level is elevated above the normal range The variations are so great, however, that it is not wise to depend upon this determination for a diagnosis

SIMPLE GOITER

Iodine Deficiency —The bulk of accumulated evidence supports the hypothesis that a lower concentration of iodine exists in the soil and water of areas where goiter is endemic than in nonendemic areas Due to the different techniques employed by various investigators, however, tabular data of the iodine content of diverse regions do not always show a sharp difference in iodine content between endemic and nonendemic goiter areas The strongest evidence in favor of this theory is the fact that in regions where goiter is endemic, administration of iodine markedly lowers the incidence of the disease Although iodine is an effective prophylactic, this does not necessarily prove that the goiter has arisen initially because of inadequate iodine However, the iodine deficiency theory is well grounded experimentally and is generally accepted by most authorities Nevertheless, there are many goiters, particularly of the sporadic variety, which cannot be explained by this theory An excellent study of iodine-deficiency goiter is available [43]

There are many reports in the older clinical literature of patients with large goiters, presumably due to iodine deficiency, who developed hyperthyroidism when treated for their goiter with large doses of iodine [11] This is the so-called "Jod-Basedow" Presumably, the mechanism in such patients is that a gland which is hyperfunctional because it is deprived of iodine suddenly becomes supplied with a large amount of raw material from which it rapidly synthesizes thyroid hormone Because of the rapid turnover induced by its pre-existing stimulated state, thyroxin is secreted into the blood at a rapid rate also It is for this reason that prophylaxis with iodized salt is looked on with such wariness in some countries

Antithyroid Drugs —Certain cases of goiter may be due to the ingestion of drugs which interfere with the sy[illegible] thyroid hormone Sometimes these drugs [illegible] for the [illegible] other diseases For example, it was n[illegible] infreq[illegible] being treated for hypertension with th[illegible] [illegible]oped [illegible] hypothyroidism

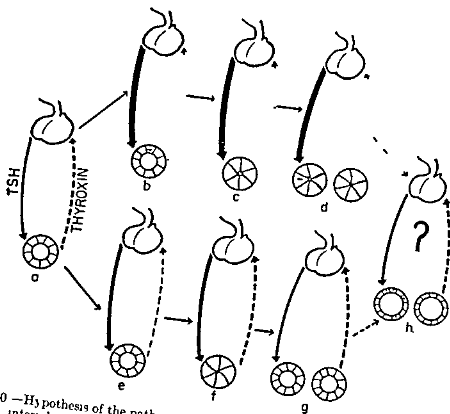


Fig 20 —Hypothesis of the pathogenesis of simple goiter [16] (*a*) The normal thyroid
pituitary interrelationship Thyrotrophin stimulates the thyroid to secrete thyroxin
which along with stimulating general cellular metabolism inhibits the further produc
tion of pituitary thyrotrophin There is thus a reciprocal relationship between the cir
culating levels of thyroxin and thyrotrophin the pituitary acting as a thermostat to
control the level of metabolism of the organism through its action on the thyroid (*b*)
If the formation of thyroxin is completely suppressed as under the continued influence
of antithyroid compounds the inhibitory influence of thyroxin on thyrotrophin syn
hesis is removed and a marked augmentation in the thyrotrophic output of the hy
ophysis is produced (*c*) This results in hypertrophy and (*d*) hyperpla ia of the thyroid
hich however is unable to increase the output of thyroxin since it continues under the
inhibitory influences initially responsible for the cessation of thyroxin synthesis The
gland will thus continue to enlarge until the limits of its growth have been reached and
a hyperplastic nonfunctioning goiter will result (*e*) If on the other hand only partial
interference with thyroxin synthesis is produced as by moderate iodine deficiency or
small concentrations of antithyroid compounds a different equence of events occurs
The thyroid gland is still able to manufacture a small amount of hormone pituitary
inhibition is not completely removed and thyrotrophin secretion does not reach the
levels illustrated in *b* *c* and *d* (*f*) Hypertrophy and hyperplasia result in an increa ed
thyroid efficiency and the gland is thus able to produce a normal amount of hormone
This results in an increased inhibition of thyrotrophin once more and eventually (*g*) a
state is attained in which euthyroid levels of circulating thyroxin and thyrotrophin
exist in the pre ence of an enlarged but not hyperplastic thyroid The gland is able to
manufacture sufficient thyroxin because of its increased number of cells These how
ever revert to a normal histologic appearance since the circulating thyrotrophin level
has been reduced to normal A balance is maintained only because an increa ed number
of thyroid cells are functioning at a subnormal rate The adju tments illustrated in
e *f* and *g* apparently occur so rapidly that no obvious hypothyroidi m is ever apparent
(*h*) The relation between colloid goiter and the 2 examples illustrated in *d* and *g* is not
clear Perhaps removal of the goitrogenic stimulus in either type will re ult in a colloid
goiter with low epithelium yet normal function if thyroid enlargement has previou ly
existed for many years It is al o pos ible that repeated cycles of hyperpla ia and re-
gres ion are more likely to result in this type of goiter The low epithelium may rep-
resent a final exhaustion of cellular capacity to respond to thyrotrophin in some in
stances If this were so the colloid goiter would pre umably be as ociated with obvi
ous hypothyroidism

It was later discovered that thiocyanate was able to inhibit the concentration of iodide ion by the thyroid gland

Sometimes antithyroid drugs are present or formed in the manufacture of certain articles The first indication of the presence of such compounds may be the increasing circumference of the necks of employees exposed to them It was in this way that the antithyroid action of aminothiazole was discovered

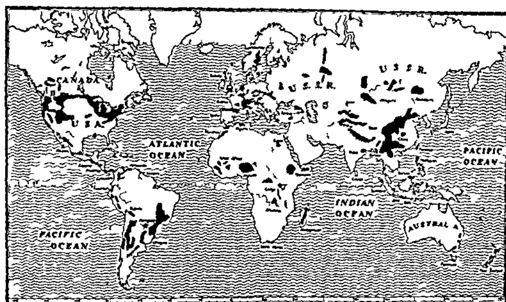


FIG 21 —Goiter areas of the world (World Goiter Survey[15])

TABLE 25 —GOITROGENIC EFFECT OF VARIOUS FOODS AS ASSAYED IN MAN BY USE OF RADIOACTIVE IODINE (MODIFIED FROM GREER AND ASTWOOD[20])

Marked effect	*Questionable effect*	*No effect*	
Rutabaga	Grape	Beefsteak	Banana squash
	Celery	Bonita	Corn
Moderate effect	Green pepper	Cheese	Rice
Turnip	Orange	Ice cream	Rye
Peach	Apricot	Lobster	Black beans
Pear	Peanut	Sardines	Lima beans
Strawberry	Pea	Shrimp	Onion
Spinach	String bean	Mushrooms	Olive
Carrot	Walnut	Dates	Almond
	Filbert	Pineapple	Apple
	Honeydew	Broccoli	Blackberry
	Cabbage	Cauliflower	Loganberry
	Lettuce	Mustard	Tangerine
	Beet	Radish	Banana
	Oyster	Cucumber	Potato
	Milk		Tomato
	Liver		
	Clam		
	Grapefruit		

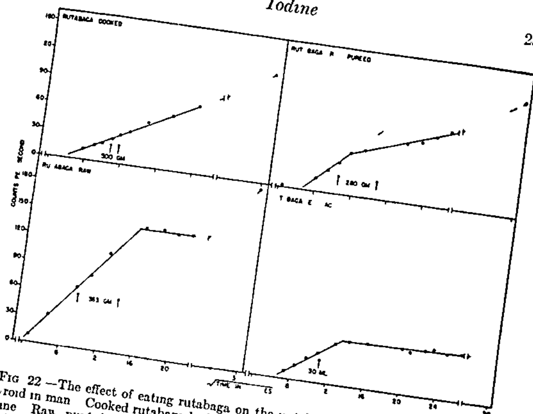


Fig 22 —The effect of eating rutabaga on the uptake of radioactive iodine by the thyroid in man Cooked rutabaga had no effect on the normal accumulation of radio-iodine Raw puréed vegetable had a moderate inhibition on uptake Raw chunks of rutabaga had a marked inhibition which lasted at least five hours A purified extract equivalent to 2617 gm raw rutabaga inhibited the uptake completely for twenty four hours

Dietary Factors —One of the oldest theories of the etiology of goiter is that it is caused by eating or drinking certain substances The first definite experimental evidence for such a hypothesis was not produced until 1928, however when Chesney Clawson and Webster discovered that feeding cabbage would produce large goiters in rabbits [9] It was subsequently found that many vegetables and especially the seeds of the cabbage family possessed the capacity for causing thyroid enlargement in laboratory animals Later studies utilizing radioactive iodine showed that certain foods seem to possess a definite antithyroid action in man The vegetables most active in this regard were rutabagas and turnips both members of the cabbage family [17] It was possible to isolate the active agent from rutabaga and from the seeds of other Brassicæ This substance is goitrin a compound related to and having approximately the same potency in man as thiouracil [3]

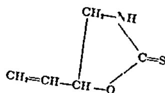


Fig 23 —Goitrin (L-5-vinyl 2 thiooxazolidone) the Antithyroid Compound of Rutabaga and other Members of the Cabbage Family

Goitrin is not present in an active form in nature It is formed by specific enzymatic hydrolysis from a thioglycoside precursor, progoitrin[18] It had been thought that the thioglycosidase responsible for hydrolysis of progoitrin was contained only in members of the cabbage family Since this enzyme is *thermolabile*, it was assumed that cooking goitrogenic foods prior to ingestion would prevent any goitrin from being liberated and thus render them innocuous Recent data have shown, however, that enzymatic hydrolysis of pure progoitrin can also take place in the intestinal tract in man Thus cooked as well as raw brassicaceous foods must be regarded *as potentially goitrogenic Certain other foods also show some antithyroid* activity, but the active material, if any, present in them has not as yet been isolated

Goiter due to eating foods containing positive goitrogens is probably quite rare Nevertheless, because of the high content of thiooxazolidone in rutabagas, it is possible that subsisting on a diet containing a high percentage of this vegetable would lead to the development of goiter[14]

Strangely enough, until recently goitrin could not be detected in cabbage, nor has cabbage ever been shown to have a goitrogenic action in man However, with the use of refined techniques it has now been possible to identify goitrin in the edible parts of cabbage, kale and related plants[46]

Biosynthetic Defects in the Thyroid Gland —In the overwhelming majority of patients with simple goiter of the sporadic variety, no etiologic basis can be assigned to their disease It is possible that in some of these patients an inherent biosynthetic defect exists in the normal chain of thyroxin synthesis and release There are at least two facts indicating that this may be so (1) Several siblings have been reported with large goiters and hypothyroidism In at least one of these groups, the normal synthesis of thyroxin did not occur[44] (2) There is a high familial incidence of goiter, suggesting that such a defect in less complete form may be carried as a recessive trait

Treatment —If iodine deficiency is the cause of the simple goiter, using iodized salt or giving small doses of Lugol's solution should lead to remission *Iodate is to be preferred to iodide in the iodination of salt,* especially in warm climates, as iodate is more stable and will volatilize less under these conditions

Regardless of the cause of the goiter, if it be assumed that the immediate cause is a relative deficiency of circulating thyroxin, supplying the hormone exogenously should inhibit the pituitary and allow maximum regression of the goiter This can be accomplished by treating the patient with desiccated thyroid Usually 60 to 200 mg daily is adequate[21]

If goitrogenic foods or the administration of antithyroid compounds can be proved responsible for the goiter, removing these items from the patient will result in a diminution of thyroid size However, if it is necessary that they be continued, the simultaneous administration of desiccated thyroid will give the same effect

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accuracy of the method with small specimens according to Bessey *et al* [13] is variable due to great technical difficulties The volatility of the solvents used, petroleum ether and chloroform, make necessary manipulations difficult and even slight evaporation of the chloroform results in condensation of moisture, with resultant turbidity from the antimony trichloride reagent Also the evanescent nature of the blue color obtained renders colorimetry very difficult on a small scale

Absorption Spectroscopy —The presence of vitamin A may be detected by its maximum ultra-violet absorption which is at 328 mu Carotene absorbs maximally at about 450 mu By comparing an unknown solution with a standard, the concentration of vitamin A or carotene in the unknown can be estimated with an accuracy of 2 5 per cent [13,14]

Utilizing this approach, Bessey *et al* [13] developed a technique which requires as little as 0 06 ml of serum The assumption is made that only vitamin A is destroyed by irradiation of the sample at 328 mu The difference in absorption coefficients before and after irradiation is a function of the vitamin A concentration The standard deviation between individual values (triplicate determinations) was 5 ug per cent for vitamin A and 7 ug per cent for carotene

Recently a critical critique of the methods and significance was published [15]

Other Methods —A micromethod for separation of vitamin A alcohol from its ester[16] and a method for distinguishing small amounts of vitamin A, its esters anhydrovitamin A, retinene and other chromagens by chromatography on filter paper impregnated with alumina[17] have also been developed

The most reliable methods for the determination of vitamin A potency are the biological assays They depend upon (1) depleting young rats of their reserves and then determining their growth response,[18] or (2) prevention rather than cure of the deficiency in rats or (3) the determination of vitamin A stored in the liver after a controlled feeding period [19]

International Units —Before the chemical natures of carotene and vitamin A were known, it was necessary to express their vitamin A activity in arbitrary biologic units Because of the small weights of material concerned and in order to include every substance with vitamin A activity, it is still convenient to use such units One international unit of vitamin A activity is defined as the quantity which is required per day to promote growth in a white rat receiving an otherwise vitamin A—free diet One international unit (*i u*) of vitamin A is equivalent to 0 344 micrograms of crystalline vitamin A acetate or 0 300 micrograms of crystalline vitamin A alcohol One international unit of carotene is the activity of 0 6 micrograms of beta-carotene [20] Dietary carotene has about half the biological activity of vitamin A This may be due to the fact that vitamin A is much more readily absorbed from the intestine than is carotene There may also be a low efficiency of conversion of carotene to vitamin A

Food Sources —Some variation in the vitamin A content of foodstuff of animal origin occurs depending upon the amount of carotene in the diet of the animal Carotene in vegetable foods, as a source of vitamin A, is much less constant The carotene content of vegetables may vary up to 10 times As a guide, the average values for milk is 4,000 i u per quart, butter 2,000 i u per ounce, one egg, 200 i u , cod liver oil, 200 to 13,000

i.u. per teaspoon, halibut liver oil 600 to 7,200 i.u. per drop, carrots, 200 to 7,000 i.u. (as carotene) per 100 grams; cabbage and green leafy vegetables generally, 1,000 to 2,000 i.u. (as carotene) per 100 gm. Vitamin A usually is added to presently available commercial margarine.

Colostrum owes its color to carotene and is much richer in vitamin A than is later milk. Summer milk may contain twice as much vitamin A as does winter milk; human milk often is richer than cow's milk. The vitamin A content of any milk depends upon the diet of the mother. The quantity of vitamin A provided by commonly used milk mixtures for infants is less than the requirement for storage. Supplements of vitamin A therefore are indicated at least until the infant begins to receive vegetables. After the first 3 to 4 months of life the intake from diet alone exceeds NRC recommended allowances with about 50 per cent coming from plant sources.[21]

Requirements.—Minimal and optimal requirements for vitamin A in man are not well established. They are influenced by many factors such as the extent of storage in the liver, the form in which vitamin A is taken, the media in which it is taken, that is, whether in aqueous dispersion or oil, the presence or absence of illness or defect in the function of the gastro-intestinal tract. One of the most significant studies is that of Hume and Krebs.[2] Sixteen adults were placed on a vitamin A and carotene deficient diet; 7 were placed on a diet containing 2,500 units of vitamin A daily. On the deficient diet, the plasma carotene content fell rapidly and approached zero levels during the first few weeks. The plasma vitamin A fell much more slowly and in one subject there was no decline for twenty-two months. The mean value of 88 i.u. per 100 ml. of plasma during the first two months of the experiment fell to 74 in nine months and in a reduced number of subjects was still 61 i.u. after fourteen months. The response of the subjects to dark adaptation showed a greater relationship to the season of the year than to vitamin A depletion. In only 3 of the subjects could failure of dark adaptation be demonstrated as significantly different from that to be expected in relation to the season of the year. These 3 subjects had 40 or less i.u. of plasma vitamin A. A daily dose of 1,300 i.u. gradually improved the dark adaptation and restored normal plasma levels in these 3 subjects. The 7 subjects who received 2,500 units of vitamin A daily developed no evidence of vitamin A deficiency and no lowering of the plasma vitamin A. The committee conducting the study concluded that a daily dose of 1,300 i.u. was sufficient to cure the deficiency and that 2,500 i.u. constituted a safe margin. The human body apparently mobilizes and expends the vitamin A reserves of the liver with notable economy during periods of vitamin A depletion. The normal liver contains about 600,000 i.u. of vitamin A.

The latest requirements of the Food and Nutrition Board of the National Research Council of the United States[3] for daily vitamin A (two-thirds of total vitamin A activity as carotene) in international units are as follows: adults 5,000; pregnancy (second half) 6,000; lactation 8,000; infants 2 to 12 months 1,500; children one to three years 2,000; four to six years 2,500; children seven to nine years 3,500; ten to twelve years 4,500; thirteen to twenty years 5,000.

The percentage of dispersing agent used, such as sorbitan polyoxyethylene laurate, has a bearing on particle size, and, therefore, may affect the rate of absorption.[41] Reduction of interfacial tension between the intestinal wall and the particle by the dispersing agent also may be of importance.

The form of the vitamin, that is, whether it is an ester or an alcohol, is of less importance than the medium in which it is administered. In the normal human, child or adult, the ester is as well absorbed as the alcohol form, when both are given in aqueous dispersion.[38]

Fat within the intestine is not necessary for the absorption of vitamin A. Addition of polyoxyethylene sorbitan monooleate ("Tween 80"—Atlas Powder Company trademark) to vitamin A ester in oil increases absorption, probably because of the ability of the monooleate to lower surface tension. In cases of sprue, cystic fibrosis of the pancreas (eccrinosis), ileitis and in patients recovering from subtotal gastrectomy the addition of this substance markedly elevates blood levels following test doses. The addition of lecithin to the diet has similar effects. Simultaneous administration of lecithin results in higher blood levels and also an increased amount in the liver. These findings may be due to the dispersing effect of lecithin. Lecithin was found to increase the vitamin A blood levels and presumably the intestinal absorption in sprue but had no effect on the low blood levels obtained in severe hepatic damage.[47]

Absorption in the very young, that is, in the newborn and the premature infant, is very slow as compared to that in older children and adults.[8, 38–40] It is even poorer in the premature infant than in the full term newborn.[39, 43, 44] Even in premature infants, absorption is improved when vitamin A is administered in an aqueous dispersion.[39, 43] In premature infants, absorption of vitamin A can be increased approximately 10 per cent by the use of either "Tween 80" or "Tween G1205".[45] Absorption in the aged, over seventy years, also is relatively slow.

In patients with cystic fibrosis of the pancreas (eccrinosis), the absorption of the alcohol form of vitamin A approximates that of the normal;[30, 39] however, absorption of the palmitate in aqueous dispersion and of the esters in oil is much lower than normal, indicating that the pancreatic enzymes are very important for the digestion of the esters.

Serum vitamin A levels following a test dose are significantly different in the different age periods, being lowest in infants under six months of age, higher in those six to twelve months of age, and highest in the older child.[39]

Ligation of pancreatic ducts in dogs[39] results in very greatly decreased absorption of vitamin A. Even with the alcohol form absorption does not approach that of the normal dog.

In contrast to vitamin A, simultaneous absorption of a certain amount of fat appears to be necessary for efficient absorption of carotene. When finely grated carrot is given to a human being on a fat-free diet, about 90 per cent of the carotene is excreted in the stool; however, when the carotene is given in oil, only about 30 to 50 per cent is excreted.

Bile is essential for absorption of carotene in animals as well as in man. The presence of bile does not appear to be necessary for proper absorption of vitamin A in animals.[9, 46] Spector *et al.*,[47] however, found that absence

of bile salts in obstructive jaundice interferes with absorption of vitamin A In this condition simultaneous administration of bile salts with vitamin A concentrate increased the blood level tenfold over that which was found when vitamin A concentrate alone was given

Vitamin A is better absorbed when administered with tocopherol Since oxidants of any sort destroy vitamin A, this is probably due to the antioxidant effect of tocopherol While high doses of tocopherol acetate diminished the storage of vitamin A in the liver and kidneys of rats fed moderate amounts of carotene, high doses had no effect on storage of vitamin A, when the preformed vitamin was fed

Vitamin A and carotene are both soluble in mineral oil which is not absorbed from the gastro-intestinal tract It has been reported that if *sufficient mineral oil is given, they are not efficiently absorbed* In 66 patients, 2,500 i u per day of carotene was sufficient to sustain a constant vitamin A serum level[48] Five cc of mineral oil (with the noon meal) was without effect while 30 cc of mineral oil (with the noon meal daily) for a period of four weeks produced a drop in the serum vitamin A concentration from about 45 ug to about 32 ug /100 cc of plasma

Thus, in normal individuals both the vitamin A ester and the alcohol are efficiently absorbed in either aqueous or oily media although they are more rapidly absorbed in aqueous media The addition of a dispersing agent such as Tween 80 ' or lecithin results in a higher blood level following test doses Since vitamin A is easily oxidized antioxidants such as bile salts and tocopherol, may stabilize it Any disease which impairs the secretion of normal pancreatic juice or the function of the intestine may interfere with vitamin A absorption Mineral oil in sufficiently high doses interferes with absorption of vitamin A and carotene

Storage and Transport —The liver contains about 90 per cent of the entire amount of vitamin A found in the body of man and of some other animals The capacity for storage by the liver is so great that in some species such as the rat enough may be stored after a single massive dose to meet the requirements for the duration of life Human livers may contain *enough vitamin A to suffice for three months to a year or more* The calculations are based upon the assumption that the vitamin will be used efficiently and that the stores will be available when needed Experiments with animals show that excessive stores are lost at a daily rate greater than the supposed daily requirements, and that small stores are lost at a daily rate less than the daily requirement Infection, poisonings (especially with liver poison) and hyperthermia increase the rate of loss

The mechanism of storage and mode of release of the vitamin are still subjects of controversy Most evidence indicates that it is stored in the liver as an ester However it has been demonstrated in rats that liver homogenates and their nuclei mitochondria and factor "X" (liver homogenates minus mitochondria and nuclei) are unable to hydrolyze the natural or palmitate esters of vitamin A (they are able to hydrolyze the acetate), suggesting that hydrolysis of these esters does not occur in the liver It would appear then that vitamin A probably leaves the liver in the ester form to be converted to the alcohol form in the circulating blood perhaps by an esterase[49]

The fetal liver contains vitamin A The total amount in the liver at birth varies considerably and is smaller in premature infants than in the mature The amount does not increase when the infant receives milk without supplements, such as cod liver oil and vegetables After such supplements a marked increase occurs It appears that neither human milk now cow's milk provides enough vitamin A to increase the stores in the liver of normal infants Since the stores at birth may be low, as in the case of premature infants, and since infections and gastrointestinal disorders may lower the stores, it seems good practice to introduce supplements of vitamin A into the diet of all infants soon after the age of 2 weeks

Practically all of the vitamin A of the blood is found in the plasma Except after the ingestion of large amounts of the vitamin, all of the plasma vitamin A exists in the alcohol form It is reported to be associated with alpha$_1$ and beta$_1$-lipoproteins of the plasma Some recent evidence suggests that vitamin A alcohol is not transported by a lipoprotein but by a protein of very high density [49] An increase of plasma vitamin A occurs after the ingestion of large amounts of the vitamin, and the increase is entirely in the ester form It is believed that the ester is on its way to the storage tissues, and that the alcohol vitamin A is on its way from the liver to the tissues where it is needed

Krause and Alberghini [49] in seeking an explanation for the preponderance of the alcohol form in the blood, found that serum contains an esterase capable of hydrolyzing the ester forms However, whether vitamin A be given as the alcohol or the ester, the rise in the blood is in the ester form Eventually the circulating ester is taken up by the liver where vitamin A is stored

Serum Levels —The normal level for serum vitamin A in adults is probably between 100 and 300 i u (approximately 30 0 to 90 0 ug) per 100 cc [39] In pregnancy the level is about 10 per cent below normal in the third trimester,[51] in the first two trimesters it is in the normal range In old people, the level is generally below normal, averaging 27 ug per 100 cc of serum (ranging from 6 to 78 ug per 100 cc) The average level at birth has been reported as between 49 and 86 i u (15 to 27 ug per 100 cc) [5, 53] In one study the serum level at birth was 76 units (24 ug), it fell to 37 (11 ug) within twenty-four hours and rose again, on the fourth day The low levels were thought to be due to the failure of immature and poorly developed livers to mobilize adequate amounts of the vitamin, and to a low intake [54]

During infections a considerable decrease occurs, dependent upon the severity *and the duration of the infection* *In lobar pneumonia*, plasma vitamin A may disappear entirely Artificial hyperthermia also causes a decrease in the plasma vitamin A Experiments with animals show that the decrease in plasma levels due to infection or to hyperthermia occurs regardless of the quantity of vitamin A in the liver [55] After the febrile period of an infection the plasma vitamin A rises, sometimes to a considerable degree In depletion tests with animals, the plasma vitamin A does not fall until the stores are nearly exhausted Only then does the plasma level of vitamin A reflect the amount in storage Determination of

the level of plasma vitamin A, therefore does not afford an estimate of the amount present in the stores

Normal and Pathologic Physiology —When deficiencies occur in nature several dietary factors may be deficient For this reason it is not always possible to ascribe the observed pathologic changes to the deficiency of a single factor In experimental deficiencies, conditions can be so arranged that pathologic changes due to a single deficiency can be induced, and the sequence of changes can be studied not only during the period of excluding them, but also during the period of recovery In the case of vitamin A deficiency, the pathologic changes are very nearly alike in many animals monkeys, cattle, swine, dogs, rabbits guinea pigs, rats mice, and fowls, and many of the conditions are similar to those which have been observed in man

Vitamin A deficiency in man[5] may be due to dietary lack to interference with absorption or storage of vitamin A to interference with conversion of carotene to vitamin A, or to rapid loss of vitamin A from the body Interference with absorption or storage has been observed in the celiac syndrome, sprue, cystic fibrosis of the pancreas ulcerative colitis, operations upon the pancreas, operations which bypass the duodenum, congenital partial obstructions of the jejunum giardiasis, obstructions of the bile ducts and cirrhosis of the liver In diabetes mellitus and in hypothyroidism there appears to be failure to convert carotene Loss of vitamin A occurs from the blood during infections such as pneumonia and scarlet fever rheumatic fever and in mild respiratory infections in children The plasma vitamin A may become undetectable and visual adaptation to dim light may become impaired These facts do not necessarily indicate exhaustion of stores Thus, with sterile abscesses in rats although the serum concentrations decrease, the liver concentrations remain unchanged[55]

Even today there are areas of endemic dietary vitamin A deficiency[57] Recent findings reveal it in unexpected peoples such as the Eskimos of Alaska[58] An important case report of a 3 month infant in the U S A should serve as a warning This allergic infant, born to a mother who was on a low fat diet was fed a soy bean milk which contained no added vitamins Both eyes were affected and vision was lost in one[59] However such deficiency is uncommon in the United States, if one relies for diagnosis upon cardinal signs (night blindness xerophthalmia and typical lesions of the skin) Dietary survey[21] indicates that after the first four months, plant sources supply an average of 40 to 60 per cent of the total dietary vitamin A and that after the first three months more than three-fourths of the children exceed N R C Recommended Allowances from diet alone Owing to lack of any definition of suboptimal health to the failure to improve health by the administration of vitamins to apparently healthy persons, and to the nonspecific character of the early signs and symptoms of any deficiency it is difficult to accept the view that vitamin A deficiency is common in the United States

Clinical manifestations of vitamin A deficiency which are nonspecific in the sense that they may be due to many other causes, are retardation of growth and lowered resistance to infection

Vitamin A is necessary for proper vision In its absence night blind-

ness" occurs The rods of the retina are concerned with vision in dim light This function depends upon the presence in the rods of a substance called visual purple (rhodopsin) In certain fresh-water fish, the function depends upon another pigment, porphyropsin The fact that faulty vision in dim light was known to occur in persons consuming diets lacking milk fat led to studies which identified the specific lack as vitamin A In a brilliant series of investigation, Wald[60] was able to show that visual purple actually contains a derivative of vitamin A, an aldehyde called retinene, combined with a protein, that, under the influence of light, visual purple breaks down into two constituents, and that, *in the dark, these constituents* recombine to form visual purple It has been shown also that porphyropsin contains a protein and an aldehyde, retinene$_2$, related to vitamin A$_2$ These observations provide a rational explanation for nutritional night blindness and a basis for its treatment

The cones of the retina have to do with color vision and with vision in bright light The cones contain a pigment, visual violet, which requires the presence of vitamin A for its regeneration, however, reports that color-blindness can be relieved by vitamin A have not been confirmed

Inability to see in dim light, accompanied by ability to see in bright light, is called night blindness Night blindness is termed "hemeralopia" whereas inability to see in bright light with ability to see in dim light is termed nyctalopia" According to their derivation, these words should mean exactly the opposite, however, the ancients used each word in both senses, and both words are now sometimes used for night blindness

Night blindness may be due to organic disease of the retina, and slightly impaired ability to see in dim light may be a fixed characteristic of an individual In general, however, the acquired *curable* condition is due to deficiency of vitamin A, and it may be the earliest clinical manifestation of that deficiency Its presence may be overlooked in a child, and in any person *if its onset is gradual and its course continuous*

Deterioration of dark adaptation is also accompanied by changes in the color sensitivity of the retina The fields for blue and red may be diminished or even inverted, and a shrinking of the field for yellow may be observed The rods are the elements responsible for light discrimination in reduced illumination However, the function of the cones may also be affected Thus concentric constriction of the visual fields may occur, a sign probably indicating involvement of the cones as well as of the rods

Night blindness may be epidemic when many persons at one time receive deficient diets Its occurrence has been reported in Negro slaves in Brazil and in Chinese soldiers The diet of the latter was rice wheat, millet, very little flour, meat once a month, and no green vegetables at all Among Newfoundland fishermen it was relieved in twelve to twenty-four hours with cod liver oil It was common during the First World War among Austrian prisoners in Russia, Austrian physicians (who were also prisoners) observed it among Russian peasants in the period of religious fasts before Easter During this period all animal food fish, eggs, milk and butter, was forbidden, the diet was strictly vegetarian Lightly cooked liver or cod liver oil were the popular remedies, the latter cured the night blindness

in two or three days. Night blindness is occasionally reported in persons whose diets are adequate in vitamin A, but who are unable to absorb it.

The person with night blindness may complain of his inability to see in the evening twilight, whereas he has less difficulty in the early morning twilight. His symptom may be noticed first after exposure to brilliant illumination. He may get some relief by wearing tinted glasses in the daytime. Street lamps may appear dim and amber colored. Coming from bright light into dim light, as in the theater, he may be unable to find his way about for five minutes or more. In dim light he is liable to bump into other persons or objects and to stumble over obstacles. He may have difficulty in driving a car. The symptoms may vary in degree from time to time.

The diagnosis of nutritional night blindness depends upon proper appraisal of the diet and of any conditioning factors if the diet is adequate, the demonstration of definitely low blood levels and upon improvement when vitamin A is administered. The presence of other signs of vitamin A deficiency is not necessary. Organic disease of the retina must be excluded. Some claim that if response to adequate treatment with vitamin A does not occur within a few days the diagnosis is unlikely. On the other hand others state that recovery is regularly slow, suggesting some deep seated lesion favored by the long continuation of a deficiency diet or by other factors.

Xerophthalmia, dryness of the cornea and of the conjunctiva, has long been recognized in association with malnutrition. It is a manifestation of severe deficiency of vitamin A. As early as 1904 a very high incidence of xerophthalmia (hikan) in Japanese children was reported and it was noted that feeding cod liver oil and chicken livers was effective therapy. The condition is relatively frequent in epidemic form also in China and India but well developed cases are exceedingly rare in the United States and have not occurred in epidemics. It occurred among infants in Denmark during the First World War when nearly all dairy products were being exported. It is commonest between the sixth and twelfth month and in early adult life. It occurs most frequently in the late winter months.

Xerophthalmia is a consequence of metaplasia of the conjunctiva causing roughness and metaplasia of the para ocular glands which leads to loss of their secretions and consequent dryness. Infection is secondary. The earliest sign is drying, roughness and wrinkling of the conjunctiva. It is followed by swelling and redness of the lids, pain and photophobia. If the lids are held open for a few minutes dry lusterless patches may be observed on the conjunctiva. At the canthi may be seen triangular whitish foamy patches—Bitot's spots. A light brown pigmentation may develop throughout the conjunctiva. The cornea loses its sensitivity and becomes clouded. Ulcers are liable to form if the condition remains untreated and softening of the cornea (keratomalacia) may occur with perforation. Panophthalmia then destroys the eye. Night blindness is present in most adults with xerophthalmia and is probably present but is not easily observed in infants. Characteristic changes in the skin are often present in the older patients. Infants affected by xerophthalmia usually are weak and wasted. Failure of conversion of carotene into vitamin A perhaps explains the

occurrences of xerophthalmia in severe hepatic insufficiency and in intestinal disturbances. Generally, disease and old age apparently can diminish the ability to transform carotene into vitamin A. In these cases carotene may fail, while vitamin A cures the condition.

The prognosis in uncomplicated xerophthalmia is good, if treatment is prompt and adequate. Otherwise, partial or complete blindness may result. Many of the younger patients die of intercurrent infections. Infants with xerophthalmia are particularly liable to infections of the respiratory system, kidney, and skin.

Prompt diagnosis obviously is essential. It depends upon correct evaluation of the dietary history and of the local signs. Although examination of scrapings from the conjunctiva has been recommended, its value is questioned. Kruse[61] has used the biomicroscope for the detection of early signs. No response or very slow response to treatment with vitamin A is evidence against the diagnosis of nutritional xerophthalmia.

Local treatment with antibacterial agents is indicated if infection is present, but vitamin A is indispensable. Given vitamin A, the luster may return to the cornea in five days and Bitot's spots may become fragmented and disappear in five or six weeks. All signs of vitamin A deficiency in the eye may disappear in two months.

An adequate supply of vitamin A is needed for growth. The mechanism by which growth occurs under the influence of vitamin A is unknown. One group found that vitamin A deficiency results in decreased utilization of nitrogen in immature but not in mature rats. This suggests that vitamin A is necessary for the growth of tissue protein, but not for its maintenance.[62] Some indirect information about its effect on growth may be deduced from the fact that the mitotic rate is reduced about 30 per cent in vitamin A deficiency. Vitamin A also influences mucopolysaccharide biosynthesis. Addition of this vitamin to cells growing in tissue culture decreases the binding of sulfate to mucopolysaccharide and changes the character of the cells.[63]

Growth of bone is retarded in young animals long before gain in weight is affected. Because the central nervous system continues to grow, the cranial cavity and spinal canal become overcrowded. All of the nervous manifestations—paralysis, and degeneration of various tracts of the spinal cord—are probably due to this cause.

In swine, partial vitamin A deficiency of the mother may result in anophthalmos and cleft palate in the fetus. In the rat, the fetus may develop congenital defects of the eyes and of the heart.

Aside from its role in growth and in vision, the vitamin is important in maintenance of epithelial structures other than the eye.

Thus, other epithelial structures may become keratinized, especially the respiratory, gastrointestinal and genito-urinary tracts, the salivary and endocrine glands and the vagina. The appearance of calcium phosphate concretions in the urinary tract may be related to keratinization of that system. This is seen especially in the tropics and the Far East, probably because of diets low in fat and fat-soluble vitamins. May[64] suggests a relationship between vitamin A deficiency and susceptibility to infection. This, in turn, may be related to the change in epithelial structures. Some

suggest that deficiency early in life may make the body more susceptible to infections at a later age

In vitamin A deficiency in rodents, the enamel organ atrophies. A similar change has been reported by Boyle[6] in a human infant with vitamin A deficiency.

A liberal intake over a long period of time has been found, in animals, to increase longevity. In some experiments, stepwise increases over the basal requirements up to fourfold increased the longevity of animals and increased the vitality of the adults as well as of their offspring. Vitamin A deficient diets in male rats lowered their resistance to x-radiation and to low environmental temperatures.

Vitamin A deficiency may result in a papular skin eruption involving the pilosebaceous follicles (phrynoderma or toad-skin).

In some cases[66] the diet had been deficient for six months to over one year before symptoms began: rice, maize, millet, a little poor grade wheat flour, white cabbage and salted vegetables—no meat or eggs, rarely green vegetables. The two youngest patients in one study were 4 and 5 years of age; most of the patients older than 16 years were males. Skin lesions preceded ocular lesions when the latter occurred.

The dermatosis begins with dryness and roughening and itching of the skin of the whole body. Eruptive lesions appear suddenly at the site of the hair follicles as dry, firm, pigmented papules about 5 mm. in diameter with a central protruding keratotic plug or spine situated below the follicle. The lesions begin on the anterolateral surface of the thighs and the posterolateral surface of the upper forearms and spread. Pustulation occurs in one-third of the cases. The skin assumes a slatey grey color. Comedones are frequent on the face and chest. Histologic studies reveal atrophy of the glandular tissue and hyperkeratosis. Other manifestations of vitamin A deficiency may be present. The absence of xerophthalmia may indicate a particular predisposition of the skin. Night blindness has been common in some studies.

The dermatosis responds to moderate amounts of vitamin A, slowly to adequate diet alone. When given 50,000 units of absorbable vitamin A per day, the patient's skin becomes soft and moist in two weeks, xeropthalmia if present disappears in a month, exfoliation of the papules and extrusion of the hyperkeratotic plugs occurs occasionally in a month, and a cure is complete in two or three months. Slight scarring may persist. One patient was cured in fifty-one days when 1 or 2 mg. of carotene was added to his usual diet, indicating that the dermatosis was due to vitamin A deficiency alone. Daily doses of 100,000 to 200,000 I.U. of vitamin A have been used. In these instances it possibly functions as a pharmacologically active drug rather than as replacement therapy.[67] Large doses of vitamin A alcohol in water dispersion may be indicated when the deficiency is due to poor absorption.

Large supplements of vitamin A given during pregnancy do not affect the vitamin A level of the infant.[5, 53, 68] Some could find no relationship between the levels of vitamin A and carotene in the mother and fetus and some concluded that placental transfer was unclear.[52] Others found that carotene in the fetal plasma varied regularly with the carotene in the

maternal plasma and concluded, therefore, that carotene is transferred but vitamin A slightly or not at all[53] Bovine fetal liver has been found to to have a vitamin A content in direct relationship to the mother's diet, which suggests that the conflicting results on the relationship between vitamin A and fetal and maternal plasma may be due to variations in the rate at which the fetal livers remove vitamin A from the blood[69] Newborn calves were found to have very little stored vitamin A, when their mothers had been fed carotene, but feeding 1,000,000 U S P units of vitamin A to the cows produced calves with much higher stores of vitamin A and carotene in the blood and liver[70] The evidence suggests that, when pregnant humans or cows or other animals are fed high doses of vitamin A until higher blood levels are reached, there is a higher store of vitamin A in the liver of the offspring If pregnant rats are fed cholesterol, the placenta becomes very fatty and the fetus contains much less vitamin A

Both in the human and the cow, the concentration of vitamin A in milk is closely related to the concentration in the blood About 85 to 93 per cent of vitamin A in milk is in the ester form and only about 8 per cent is in the alcohol form

In young animals on a vitamin A deficient diet, the skeleton ceases to grow before any of the other tissues of the body The most obvious effect of vitamin A deficiency upon bone growth in the chick (as in mammals) is upon epiphyseal cartilage sequences and endochondral bone growth The tunneling of the epiphyseal cartilage is irregular, often forked or branched, and less extensive The zone of proliferating cartilage cells is less clearly demarcated and cells in mitosis are absent The compact bone becomes cancellous so that there is an overgrowth and an increase in thickness, though not in calcium content The distribution of osteoclasts and osteoblasts in the skull and vertebral column is altered, the two kinds of cells may even change places Vitamin A deficiency also greatly delays the repair of fractures in rats The deficiency may result in impaired epiphyseal bone formation, and faulty formation of odontoblasts may lead to deranged tooth formation

Numerous studies have indicated a relationship between vitamin A metabolism and the endocrine system Large doses of vitamin A cause a fall in thyroid weight and iodine content of rats, a fall in hepatic iodine and a rise in the iodine content of serum, muscle and pituitary Hypervitaminosis A leads to thyroid atrophy while vitamin A deficiency leads to hypertrophy Haubold[71] suggested that a wave of goiter among children in the mountainous parts of Germany might have been caused by a deficiency of carotene In a survey of two nearby villages he found that in one, where sources of vitamin A were abundant, the incidence of goiter was low, in the other village, where the sources of vitamin A were scarce, the incidence of goiter was about doubled The hyperplasia and hyperemia of rat thyroids caused by thiouracil is decreased by the simultaneous administration of vitamin A Cows fed thiouracil excrete more carotene in their feces and those fed thyroxin excrete less The administration of thyroxin or thiouracil to rabbits does not affect the blood level of vitamin A

The thyroid hormone appears to be necessary for conversion of carotene to vitamin A Night blindness frequently occurs in hypothyroidism In

one survey, the livers of patients dying of thyrotoxicosis were found to contain more vitamin A than any other human livers[7] The cretin shows an inability to convert carotene to vitamin A[73] Patients with untreated myxedema are likely to have high blood carotene levels Dinitrophenol increases the basal metabolic rate and there are conflicting data regarding its effect upon liver deposition of vitamin A Vitamin A administration reduces the weight of the thyroid gland in normal and in thiouracil treated rats It reduces the increased BMR caused by thyroid administration, and in large doses appears to have a direct inhibitory effect on the thyroid gland Vitamin A was found to depress thyroid tissue respiration in rats Studies with radioactive iodine show that vitamin A deficiency reduces the rate of formation of thyroxin

Wendt[74] found that vitamin A and thyroxin have an antagonistic effect Administration of large doses of vitamin A resulted in relief of symptoms and decline in the basal metabolic rate in a patient with thyrotoxicosis The author has not had similar success in treatment of two children with hyperthyroidism with large doses of vitamin A for short periods (two weeks)

The testicles of vitamin A deficient rams are undersized and the initial motility of the spermatozoa is reduced[73] These defects could not be corrected by the administration of testosterone However androgens can be produced by the testes of vitamin A deficient rats when gonadotrophic hormone is administered[74] In view of these findings it seems likely that the effect of vitamin A deficiency on the gonads lies in its primary effect on the pituitary

When testosterone or stilbestrol are administered to patients with carcinoma, the serum vitamin A rises If female dogs are injected with testosterone the serum vitamin A level falls

Vitamin A deficiency in rats causes delayed and irregular estrus In the vagina hyperplastic changes occur whereas in the uterus there is keratinizing metaplasia The latter may be due to a balance between estrogen and the vitamin since this does not occur in ovariectomized animals unless estrogen is given[7] Direct effects of vitamin A on the growth and development of the ovary have been noted Others have found prolonged gestation and difficult parturition in vitamin A deficient rats

That diabetics have a relative inability to convert carotene into vitamin A has been reported by some and denied by others

Recently evidence has been presented that a deficiency of vitamin A interferes with production of cortical steroids Adrenals from vitamin A deficient rats had marked decreased ability to produce these steroids but this could be raised almost to normal by injection of the vitamin two hours before removal of the glands Further it has been shown that, upon giving radioactive labeled acetate to vitamin A deficient rats a severe block in glycogen labelling results The defect occurs somewhere in glucose biosynthesis from triose and is indirect *i e*, dependent upon lack of corticosterone and therefore hormonal rather than due to an enzyme lack[8-9]

Vitamin A in large doses increases urea clearance of rats, dogs and man This is probably due to increased renal blood flow and increased glomerular filtration demonstrated with very large doses of vitamin A (200 000 units

daily) administered to dogs The increased urea clearance could not be maintained for over one hundred and twenty-eight days in the dog

High fasting serum vitamin A levels are found in children with the nephrotic syndrome[80] Following oral test doses, the levels rise much higher than in normal children and remain higher for a longer period of time The concentration of vitamin A in the liver in this syndrome is also abnormally high[81] It has been suggested that the liver in this condition is failing to store or release vitamin A in a normal manner Bilateral nephrectomy, in short term experiments with rats, had no effect on liver or blood vitamin A concentrations[82]

Widespread degeneration of the medullary sheaths of peripheral and cranial nerves and of the central nervous system occurs in vitamin A deficiency in young animals Progression can be stopped by adequate administration of vitamin A There is very slight difference between the amount of vitamin A which protects the nervous system and that which allows degeneration

The neurological degeneration is thought by some to be caused by an overgrowth of the bone surrounding nervous foramina, causing a compression of these nerves Others believe that in this deficiency, the skeleton ceases to grow while the nervous system continues to grow so that it becomes compressed by its own relative overgrowth

Internal hydrocephalus and an increase in spinal fluid pressure have been reported as due to vitamin A deficiency

Both in humans and rats, deficiency causes a mild leukopenia with decrease in polymorphonuclear leucocytes and an increase in the number of juvenile forms Administration of vitamin A causes a gradual return to normal within a few weeks Interference with function of the reticulo-endothelial system results in elevation of blood vitamin A and decrease in liver content, suggesting that this cellular system may play a role in the transfer of the vitamin from the blood to the liver store[83 84]

The ultimate fate of vitamin A in the body is not known It is found in feces, but whether it is excreted into the intestinal tract is not known It is not found in normal urine except in the dog The only body secretion in which it appears in proportion to the blood level is milk

Special tests for vitamin A deficiency include quantitative measurement of dark adaptation, tests for blood levels of vitamin A and vitamin A absorption tests

Wide physiologic variations in light sense occur There are individuals with a normal blood level of vitamin A who have a physiologically low sense of light which cannot be improved with vitamin A Moreover, psychic factors age fatigue, depression, or ocular lesions all play a part The dark adaptation test cannot, therefore, be used as a reliable test for vitamin A deficiency Also only when blood vitamin A concentrations fall below a certain limit is there a measurable deficiency in the sense of light, subjective night visual disturbances begin with much lower blood vitamin A levels

With normal blood values, the light sense usually is good Of subjects with normal average values of light sense, a rather small percentage improves on vitamin A therapy These individuals have probably an excep-

tionally good light sense and happen to suffer from a very slight degree of vitamin A deficiency.

Measurement of blood plasma or serum levels is helpful when the intake of vitamin A has been deficient or in excess. Measurement of blood levels following administration of test doses often gives even more information.

Significant information has been obtained by measuring the quantity of vitamin A or of carotene eliminated in the feces after the ingestion of known amounts of these substances. It is assumed that the difference represents the amount of vitamin A or of carotene absorbed. No carotene is ever lost in the urine, no vitamin A is lost in the urine excepting in pregnancy, in fevers, and in some cases of chronic nephritis, and then only in traces. Loss through the skin has not been measured, although it does occur in seborrheic dermatitis and in hypervitaminosis A. Destruction of vitamin A or of carotene may occur in the intestine if unsaturated fatty acids are undergoing oxidation there. The results of this method must, therefore, be interpreted with caution. The method has demonstrated that mineral oil present with carotene considerably decreases the absorption of the latter, that the cooking of vegetables increases the absorption of their carotene, that small quantities of vitamin A and of carotene are more completely absorbed than large quantities, and that the presence of fat improves absorption, especially of carotene.

In animal experiments, increase of vitamin A in the liver after oral administration of varying amounts of carotene or of vitamin A is taken as a measure of absorption.

Information regarding absorption of vitamin A can also be obtained by blood analysis after ingestion of standard doses of vitamin A. As performed in the author's department, the subject is given 12 000 i.u. of vitamin A per kilogram body weight. Blood levels are determined before the test dose, 3, 6, 24 hours later, and at other intervals when specially indicated (e.g. 48 hours in the nephrotic syndrome). The maximal rise occurs in normal persons at three hours and it may be delayed in abnormal persons often as much as six hours and sometimes 24 hours. The level at twenty four hours usually is slightly above the fasting level[39]. The highest mean concentration in older children, with vitamin A palmitate or alcohol in aqueous dispersion, is at 3 hours (3000 i.u., SD 1200); at 6 hours it is 1000 i.u., SD 500, and at 24 hours 200 i.u., SD 80. The fasting levels were 125 i.u., SD 35. Normal values vary with age, being lowest in infants under 6 months of age, higher in those 6 to 12 months of age and highest in the older child[39]. They are lower again in old age. In infants under one year of age and even more in those under six months of age, the alcohol form gives rise to higher blood levels than does the palmitate[39]. During the test it is not necessary to discontinue meals, but obviously no vitamin A, or food of high fat content such as cream, deep fry goods, etc., should be given.

Absorption tests are of importance in the study of persons who are suspected of having poor absorption of vitamin A from whatever cause. Persons with infectious hepatitis do not absorb vitamin A esters well while the stools are acholic, unless bile salts are administered. If bile salts are administered together with vitamin A, extraordinarily high levels are

observed in the plasma. This phenomenon is probably due to a slower than normal rate of deposition of vitamin A in the liver; it may, therefore, indicate impairment of one of the functions of the liver.

In cystic fibrosis of the pancreas, there is a striking difference in absorption of the alcohol and the palmitate forms in aqueous dispersion, the alcohol being much more rapidly absorbed.[30,37,39] The palmitate in aqueous dispersion and the natural esters are both relatively poorly absorbed in this condition. Persons with celiac disease or with sprue absorb vitamin A ester or alcohol poorly from preparations either in oil or in aqueous dispersion. The test, therefore, has diagnostic value, and may be of aid in selecting the suitable dosage form in treatment.[30,37,39]

Other conditions in which the absorption of vitamin A is decreased are malnutrition following prolonged infections or following diets deficient in vitamin B complex, and ulcerative colitis. In these conditions disorders of motility of the upper small intestine may be present and may be the explanation. Giardiasis[85] may interfere with absorption of vitamin A; it occasionally causes symptoms of the celiac syndrome. After adequate treatment with atabrine the giardia and the symptoms disappear, and the vitamin A absorption curves become normal.

In the nephrotic syndrome, the highest levels following test doses have been found. The explanation for this is not clear. It may be due to a defect in liver function, to an abnormal state or chemical form in the blood, or to abnormally poor utilization. The liver vitamin A in this condition is also the highest recorded.[81] Although the blood levels in nephrosis are similar to those in hypervitaminosis A, there is no evidence of vitamin A poisoning in cases of the nephrotic syndrome.[39]

Therapy.—The materials available for the prevention and cure of vitamin A deficiency include foods, fish liver oils, concentrates derived from them, preparations of carotene in oil, and synthetic forms of vitamin A, usually made available as the palmitate or stearate ester but also in the acetate or alcohol form.

The usual food sources already have been described. Ordinary mixed diets which include the usual amounts of these foods amply meet the daily requirements of vitamin A. Healthy persons do not need any other sources. Some milk substitutes, such as soybean milk, sometimes contain insufficient vitamin A, and serious results have been observed in this country when this vitamin has not been added.

Fish liver oils and concentrates derived from them are so standardized that the dosage-forms provide not over 10,000 i.u. of vitamin A per day. All of these preparations contain vitamin D also.

Viosterol in oil and water-miscible preparations of crystalline vitamin D contain no vitamin A. Polyvitamin mixtures usually contain adequate amounts of both vitamins A and D. Solutions of vitamin A in a solvent such as propylene glycol containing a stabilizer are available; when mixed with water or milk, a very fine dispersion of vitamin A is formed. Aqueous dispersions made with agents such as the Tweens are in common use today.

Carotene in oil furnishes 7500 i.u. of vitamin A per Gm.

When dietary deficiency cannot be discovered in a person with signs of vitamin A deficiency, other factors such as poor absorption may be re-

sponsible They should be treated as already described If the diet has been deficient, it is necessary not only to prescribe an adequate diet, but also to get the patient to eat it and to continue to eat it after recovery This may require economic and psychologic measures

Diet alone will, of course, cure dietary vitamin A deficiency In severe deficiency, a rapid cure by giving large doses of vitamin A is desirable In those individuals who are more likely to take prescribed medication than to follow dietary directions, and under circumstances where adequate diet is unobtainable, preparations of vitamin A must be used

A review of published experience in the treatment of all forms of vitamin A deficiency shows that response to a daily dose of 30 cc of cod liver oil (25,000 i u of vitamin A) is usually as rapid as the response to larger doses This amount of cod liver oil (30 cc) contains 2500 units of vitamin D an amount which usually is harmless If however, 100 000 units of vitamin A per day are prescribed in the form of haliver oil with viosterol oleovitamins A and D, or percomorph liver oil, then 15,000 to 26,000 units of vitamin D also are being prescribed This amount of vitamin D could be dangerous for some children It would be wiser to give haliver oil or a preparation rich in vitamin A and poor in vitamin D Preparations containing only vitamin A also are available

If pathologic changes fail to respond after two months of treatment with vitamin A, the failure may be due to poor absorption or to the condition being complicated by other factors or being due entirely to another cause When due to poor absorption, the best absorbed form of vitamin A in most conditions, the alcohol form in aqueous dispersion should be tried Examples of complicating factors and other conditions are renal lithiasis and hyperkeratosis pilaris

Healthy persons need no supplements of vitamin A provided they receive an adequate diet Infants, particularly those of low birth weight such as premature infants, need supplements of vitamin A from the age of two weeks until they begin to get vegetables Those concentrates which provide adequate amounts of vitamin D generally provide enough vitamin A After vegetables enter the diet, additional sources of vitamin A are not always necessary, but they are desirable if it is thought that the stores have been depleted by disease Vitamin D also is required during the entire growing period For the very rare infant found to be sensitive to fish liver oils carotene in oil and some preparation of crystalline vitamin D, or the generally available synthetic preparations in aqueous dispersion, or propylene glycol, is desirable The vitamins are best given with meals The vitamin-containing oils should not be mixed with the formula for an infant, because they tend to cling to the surface of the bottle or the nipple Carotene in oil should not be given together with mineral oil which prevents its absorption The newer preparations of vitamin A in aqueous dispersion or propylene glycol may be placed directly into the infant s milk

In persons subject to poor absorption or utilization the underlying condition must be treated when possible

In cystic fibrosis of the pancreas the dose should be double that of the normal and the ester forms or, preferably, the alcohol form in aqueous dis-

persion should be given. The alcohol form, being less stable, is not generally available.

In celiac syndrome (including vitamin B deficiency), and in sprue, both endemic and sporadic, probably the most effective preparations of vitamin A are the fine aqueous dispersions of either the alcohol or ester form, however, large doses of ordinary concentrates cause demonstrable increases in blood vitamin A. The syndrome itself should be treated by the administration of a high protein diet, vitamin B complex, liver extract and by reduction of gluten, starch and fat intake.

Hypervitaminosis A.—When growing rats are given large amounts of vitamin A (40,000 i.u. per day) loss of weight, soreness of the eyes, atrophy of the skin and loss of hair, decalcification and spontaneous fracture of bones and hemorrhage result. These are accompanied by decrease in plasma prothrombin and by disappearance of the ascorbic acid of the tissues. The amount of vitamin A needed to produce hypervitaminosis A in rats is approximately 10,000 times the requirement.[86]

A number of cases of hypervitaminosis A in humans have been reported since concentrates have become available.[87–90] The symptoms are hard, tender lumps in the extremities and cortical thickening of underlying bones. Additional findings in some patients include fissures of the lips, loss of hair, dry skin, jaundice and hepatomegaly. The symptoms become clinically evident six to fifteen months from the beginning of excessive vitamin A intake. The clinical signs subside within seventy-two hours following withdrawal of vitamin A. The blood levels fall in six weeks and cortical hyperostoses are gradually and slowly resorbed over a period of several months.

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VITAMIN D

By B M KAGAN

IN 1807, over a century ago Dr Bardsley of Manchester, England, wrote of the efficacy of cod liver oil for osteomalacia[1] Palm,[2] in 1890, suggested that sunlight possessed anti rachitic action In 1919, Huldchinsky[3] cured rickets with ultraviolet rays from a mercury vapor lamp In 1922 McCollum[4] and his associates provided final proof of the existence in cod liver oil of two vitamins They did this by subjecting the cod liver oil to oxidation One of the vitamins was vitamin A and McCollum proposed that the factor left undestroyed by oxidation be called Vitamin D

There are more than ten substances which possess vitamin D activity, or in other words are capable of preventing or curing rickets Of these, the two most important are vitamin D (calciferol) and vitamin D_3 *Vitamin D is formed by ultraviolet irradiation of ergosterol* $C_{28}H_{43}OH$, a substance found only in lower plants such as yeast, and fungi (ergot) Vitamin D_3 is the naturally occurring substance found in egg yolk, butter and fish liver oils It is formed from 7-dehydrocholesterol (provitamin D_3), $C_{27}H_{43}OH$, which is present in the surface of the skin Under the influence of ultraviolet radiation, it opens one of its rings to produce vitamin D Provitamin D_3 appears to be formed in small amounts from cholesterol in the intestinal wall of the guinea pig[5] There appears to be no difference in the effectiveness of D_2 and D_3 in human physiology[6] although there are some differences in toxicity in man and animals Curiously, however, vitamin D_3 is far superior to vitamin D in preventing and curing leg weakness in chickens Conversion of the provitamins to vitamin D occurs upon exposure to ultraviolet light, cathode rays, *x*-rays, radium emanation, electric currents of high frequency and electrons Dihydrotachysterol or AT 10 (anti tetany cpd No 10) is a derivative of ergosterol although it is more closely related structurally to calciferol It has only a small fraction of the anti-rachitic potency of calciferol yet retains the ability to raise calcium levels of the blood[7]

Vitamin D

The biological activity of a preparation of vitamin D is measured by its capacity to cause calcification in rachitic rats under certain standard conditions. This is known as the "line test."[8] Chemical analysis of vitamins D has been accomplished by Green.[9–13] The considerable activity in the fields of synthesis, potency and methods for analysis has been subject to recent review.[14]

The international unit was defined in 1949 as the biological activity of 0.025 micrograms of pure crystalline vitamin D_3. One U.S.P. unit of vitamin D is equivalent to 1 international unit. In pure state the vitamins D are white, odorless crystals, soluble in fats and in organic solvents and insoluble in water. They have a characteristic absorption spectrum with one maximum at 265 millimicrons. Vitamin D is heat stable. Some destruction may occur if the carrier fat becomes rancid. Vitamin D_2 is somewhat more stable than vitamin D_3. The esters of each are more stable than the alcohol forms over long (five year) periods of storage.

The minimal human requirement for vitamin D, like that for vitamin A, is not well established. The latest recommendation of the Food and Nutrition Board of the National Research Council of the United States[15] lists the minimal daily requirement as 400 I.U. for infants and children and adolescents up to twenty years of age. A similar amount is recommended for pregnant and lactating women. In a study by Shelling and Hopper[16] approximately 3000 I.U. of viosterol (D_2) daily for a period of three to four months was recommended for premature infants and any other infant growing at a rapid rate. There is no indication that adults leading an active, vigorous life require any supplemental vitamin D, unless their activity is such as to shield them from sunlight.

As a guide, the average vitamin D content of certain foodstuffs is as follows: cod liver oil 500 I.U. per drachm, halibut liver oil 50 I.U. per drop, fresh milk usually less than 100 I.U. per quart, butter 10 to 100 I.U. per ounce, eggs 60 I.U. per yolk of 20 grams. For comparison, 1 mg. of vitamin D_2 (calciferol) contains 40,000 I.U. Human blood contains about 100 I.U. per 100 cc. The vitamin D content of milk, butter and eggs depends upon the vitamin content of the diet of the animal and the season, being higher in summer than in winter. It is practically absent from vegetable oils such as olive oil and pure vegetable margarines. Most commercially available cow's milk today has been fortified so as to supply 400 I.U. per quart. It is possible for an infant receiving 1.5 pints of fortified milk, 1 ounce of fortified cereal and one teaspoonful of fortified cod liver oil to have a daily intake of about 4,000 I.U., which is excessive.[17]

Ingested vitamin D is absorbed with food fats, and any conditions which interfere with fat absorption also interfere with the absorption of vitamin D. It is stored chiefly in the liver, but it is also found in the skin, brain, spleen and bones.[18–20]

Vitamin D increases calcium and phosphate absorption from the intestine. Harrison and Harrison,[21] using radioactive calcium, studied the effect of vitamin D on calcium absorption in rats. They found that when calcium was administered as the chloride the absorption in the proximal portion of the intestine was not influenced by vitamin D (orally administered)

but that absorption from the distal third of the small intestine and from *all* the large intestine was markedly increased by vitamin D

Vitamin D causes an increase in rate of reabsorption of phosphate by the renal tubules On low phosphorus diets, it also induces utilization of phosphorus by bone at the expense of the soft tissues

Vitamin D is necessary for the formation of normal bone and for the calcification of rachitic bone The mechanism of its action is still unknown Cohn and Greenberg,[27] using radioactive phosphorus, present indirect evidence that transfer of phosphorus from blood to the organic fraction of bone is independent of vitamin D and that vitamin D acts to aid the conversion of organic to inorganic phosphorus in the bone Alkaline phosphatase may possibly be related to the action of vitamin D on bone[6] This enzyme can change organic phosphorus to inorganic phosphorus The increase of alkaline phosphatase in the blood is one of the first signs of vitamin D deficiency Harrison and Harrison[23] found, using radioactive calcium, that bone calcium in young rats was rapidly exchangeable with body fluid calcium and that this exchange was increased by the oral administration of vitamin D The rate of calcium exchange was not appreciably influenced by changes in dietary calcium intake

Vitamin D deficiency in the human may result from inadequate intake and/or from lack of sunshine In children rickets and sometimes tetany follow and, in adolescents and adults, osteomalacia Lack of mineralization is the primary disturbance due to lack of calcium and phosphorus in the blood Insufficient vitamin D results in inadequate absorption of calcium and phosphate from the intestine and excessive loss of these substances in the feces The calcium and/or phosphate level of the serum falls The calcium can be reduced to the tetany level while the phosphorus level remains relatively constant Normally the product of serum calcium times serum phosphorus, each expressed in milligrams per 100 ml of serum, is about 60 In rickets it is often 40 or less The degree of decrease may be regarded as a reliable criterion of the severity of the disease The result *is that the bones are supplied with blood deficient in minerals necessary* for calcification Consequently they become soft and irregularly formed

In rickets, *ossification at the epiphyseal line takes place in an abnormal* manner Normally this line is a well-defined narrow strip of cartilage about 2 mm deep behind which regular ossification proceeds In rickets this line becomes wide and irregular It can often be felt as a marked enlargement on the skin surface Normally the older cartilage cells degenerate and disappear leaving many spaces in which blood vessels and osteoblasts of the shafts can penetrate In rickets this preliminary degeneration does not occur and ossification is thus retarded The cartilage cells persist and go on multiplying giving rise to a characteristic broad irregular cartilaginous zone In addition, the matrix between the cartilage cells and that of the new bone itself does not become adequately impregnated with lime salts, accounting for softness of the b[illegible] When vitamin D is given in the presence of rickets, the ma[illegible] arranged cartilage cells of the epiphysis are reduced in a[illegible] the normal, short, orderly, parallel c[illegible]

Vitam[illegible] associated [illegible] in [illegible] metabolism

Almost 70 per cent of the body's entire store of citrate is in the skeleton. Dickens[24] observed a reduction of nearly 50 per cent in the bones of a rachitic kitten. Waasjo and Leg Larsen[5] showed that in vitamin D treated rachitic rats, the citric acid content returned to normal sooner than the ash content. The average serum citrate level of 10 rachitic infants was found to be 1.5 mg. per 100 cc. as compared to 2.5 mg. per 100 cc. in normal infants.[6] Following massive intramuscular injections of vitamin D (single dose of 600,000 units or two doses totalling 1,200,000 units) in rachitic infants the serum citrate rose progressively, rising above normal levels and returning to normal levels. The increase in serum citrate parallels other effects of vitamin D therapy, i.e., increase in serum calcium and phosphorus concentration and healing of bone lesions as demonstrated by x-ray examination. Nevertheless, recent evidence suggests that the antirachitic action of vitamin D and its effect upon citrate metabolism can be separated. The biochemical mechanism of the interrelation of vitamin D and citrate metabolism is still unexplained.

Rickets usually manifests itself clinically at about six months of age. Its degree of severity is directly related to the rapidity of body growth. It tends to be more severe in the prematurely born infant.[16] In addition to rapid growth, one contributing factor for this is that the fetus accumulates over 85 per cent of its calcium stores during the last three months of intrauterine life. The calcium stores of the premature infant are therefore incomplete.[28] Evidence is conclusive that rickets is due in most infants to lack of vitamin D.[28] Spontaneous healing of the disease usually occurs before the age of two as far as obvious clinical signs are concerned. However, Follis *et al.*[29] found histologic evidence for rickets in almost half the children from two to fourteen years of age seen at autopsy in a Baltimore hospital. In these cases the roles of vitamin D deficiency and mineral deficiency were not clear.

Gerstley *et al.*,[30] studying the influence of dietetic components upon calcium and phosphorus metabolism independent of the influence of vitamin D in the first six months of life, concluded that human milk is not rachitogenic while undiluted cow's milk is, especially during the winter. This is of particular interest, since both milks contain very little vitamin D. (There are only 0.42 U.S.P. units of vitamin D per 100 ml. in human milk and 2.36 in cow's milk.[31]) There may be, therefore, some factor other than vitamin D in human milk, such as perhaps the ratio of the calcium to phosphorus concentration and its relationship to the protein concentration, which may be of equal importance to the intake of vitamin D *per se*.

In the newborn, when no vitamin D was given, the incidence of hypocalcemia was reported to be 16 per cent. When 3000 units were given, it was only 2 per cent and when 45,000 units were given it was 30 per cent. This paradoxical situation has been explained as the action of vitamin D in diminishing the secretion of an already poorly functioning parathyroid gland and thus decreasing the serum calcium levels. On the other hand massive doses of the vitamin increase absorption of calcium and perhaps also of phosphorus, and also mobilizes it from the bones.[32]

Refractory rickets may extend or become apparent in later childhood although it is usually manifest in the second year.[33,34] It appears often as

due to a single dominant gene, with a variety of signs in different members of the same family. Serum alkaline phosphatase activity serves as a useful guide where other signs of the disease are absent. The clinical findings are similar to those of rickets of infancy, with bossing of the frontal bones, beading of the ribs, narrow flaring chest, prominent abdomen, swelling of the epiphyses of the wrists and ankles, bowing of the legs and pronation of the feet. Retarded growth and skeletal deformity result. It is usually differentiated from the more common privational rickets when lack of response to administered vitamin D is noted. Examples: extremely high serum D levels (20 times greater than normal) were found to be present in a boy in whom the rachitic state was first observed at the age of six,[35] suggesting poor utilization by the tissues. It was found that the administration of 1,000,000 units of vitamin D daily resulted in prompt healing of the rickets and that a daily supplement of 440,000 units was necessary for maintenance. Another similar refractory case was reported in a boy sixteen years of age in whom rickets had been present since the age of one.[36] Administration of massive doses of vitamin D (1,500,000 U.S.P. units daily by mouth) resulted in healing and a high maintenance dose was required after this. Discontinuance of therapy, even after puberty, resulted in prompt recrudescence of the disorder.

The blood phosphorus levels are characteristically low and increased tubular resorption of phosphorus follows vitamin D therapy in cases of resistant rickets. It is not known if this is the result of primary action of vitamin D on the tubules or of changes secondary to an alteration in the parathyroid glands.[37,38]

In growing children, while the bones are still developing, there is an increased need for sufficient calcium intake and utilization. Due to the rarity of clinically recognizable rickets during this age period, the need for adequate vitamin D supplementation is not always recognized. Johnston[39] studied the nitrogen and calcium balance of two girls at puberty. A definite positive correlation was observed between vitamin D intake and calcium and nitrogen balance. He suggested that a logical approach to the intake of calcium and of vitamin D is the rate of physiological growth at any age.

Deficiency of both vitamin D and of calcium in the diet may result in osteomalacia in adults. It occurs mostly under extreme conditions of famine and particularly during pregnancy. Tetany may also occur as a complication, due to low serum calcium, and may be severe. The bones of the fetuses of such patients show osteoporosis but no signs of rickets.

Park[40] reported a series of children suffering from chronic infectious diseases who developed rickets that did not respond to vitamin D therapy until the infection was over. Impaired absorption of the vitamin may have been responsible.

Low blood calcium and phosphorus levels may also result in softening of and deformity of the maxillary bones. All parts of the teeth suffer, the teeth erupting irregularly and their surfaces being rough with thin and poorly calcified enamel. Mellanby and Mellanby[41] found that, in London school children, between 1945 and 1947, increased availability of vitamin D and calcium for all children up to five years of age resulted in strikingly improved dental status.

Bread and certain cereals, especially oatmeal contain phytic acids[4] which interfere with the absorption of calcium by precipitating insoluble calcium phytate Thus, if infants take large amounts of such bread or cereal and receive a minimal intake of vitamin D or calcium, they are more likely to develop rickets

Dihydrotachysterol (A T 10) is used in hypoparathyroidism It is more toxic than vitamin D but is also more effective and more rapid in causing a rise in serum calcium An initial dose of 1 to 4 cc of the solution and maintenance dose of 0 3 to 0 5 cc is recommended in hypoparathyroidism

Large doses of vitamin D have been used in recent times in the treatment of a number of diseases (rheumatoid arthritis lupus vulgaris psoriasis pemphigus tuberculosis, etc) Toxic effects have been observed in adults[43 44] receiving 100,000 or more i u daily for several months and in children receiving 40 000 i u daily[4] The effects resemble those of parathyroid hormone overdosage The symptoms are principally anorexia nausea, vomiting diarrhea, headache drowsiness polyuria and polydipsia The serum calcium and phosphorus levels are increased and correspondingly high concentrations are found in the urine Calcium may be deposited in the heart, large blood vessels, lungs renal tubules and other soft tissues[46] Signs of renal failure and hypertension may develop Osteoporosis occurs as a result of osteoclastic resorption with the simultaneous massive deposition of calcium in other tissues[47] The effects are reversible if vitamin D administration is stopped in time[43] Anemia in some humans has been attributed to high intakes of vitamin D[48] Whenever giving a child over 40,000 i u or an adult over 100,000 i u close observations should be made including frequent examinations of the urine and of the serum calcium

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VITAMIN K

By B M KAGAN

In 1929, Dam described a hemorrhagic disease in chicks raised on fat-free diets[1] Later he showed that this was due to a specific dietary deficiency[2] Dam called it vitamin K to indicate "Koagulationsvitamin"

Vitamin K is found principally in leafy vegetables and is especially plentiful in alfalfa[3] It was isolated from the latter in 1931[4] Another compound which was equally active but with different physical characteristics was recovered from putrified fish meal and in microorganisms[4] These were called respectively K_1 and K_2 Soon thereafter the constitution and synthesis of vitamins K_1 and K_2 were determined[5-9]

Natural vitamin K_1 is 2-methyl-3-phytyl-1, 4-naphthoquinone

$$C-CH_2-CH=\underset{CH_3}{C}-(CH_2)_3-\underset{CH_3}{CH}-(CH_2)_3-\underset{CH_3}{CH}-(CH_2)_3-\underset{CH_3}{\overset{CH_3}{C}}-H$$

Natural K_2 has a difarnesyl group instead of a phytyl group K_1 and K_2 are soluble in fat solvents but are insoluble in water They can be given

by mouth or intramuscularly A preparation of vitamin K_1 oxide[10] or K_1[11] in aqueous colloidal solution can be given intravenously[10] Many substances of related chemical composition with variable vitamin K activity have been synthesized The most potent is 2-methyl-1, 4-naphthoquinone (menadione, U S P) Vitamin K_1 can be synthesized from this compound[8] Water soluble analogs have been prepared which can be administered intravenously

Analytical methods for vitamin K have been reviewed by Dam[11] The basic method for measuring vitamin K is biological assay on the chick Vitamin K-deficient chicks are fed the test material[1] The clotting power is determined twenty to twenty two hours after the injection of a single dose of the test material Menadione in oil solution serves as the standard

Vitamin K is widely distributed in nature It is found in traces in green vegetables, cereals and animal tissues generally It can be synthesized by many bacteria including those normally present in the human intestine Normally the bacterial flora of the intestine provide an adequate supply of vitamin K in humans Infants probably do not have an adequate supply of vitamin K from this source until the third or fourth day of life since the bacterial flora of the intestine have not had sufficient time to develop Supplementary vitamin K is generally recommended at birth

An adequate supply of bile salts is necessary for absorption of the vitamin from the small intestine It is absorbed into the lacteals and passes thence into the thoracic duct[13 14] In the liver it plays an indispensable role in synthesis of prothrombin although it is not incorporated in the prothrombin molecule

There is some experimental and clinical evidence that the physiological action of vitamin K_1 and the synthetic menadione are not identical When C^{14} menadione was given intramuscularly to mice the radioactivity was found to be rapidly removed from the injection site and excreted in the urine[15] None was stored in any tissue or remained for any length of time in the blood Similarly labelled vitamin K_1 remains in the body for a considerably longer time[16]

Following the action of Dicumarol a single dose of vitamin K_1 given intravenously decreased the prothrombin time to safe values within six to seven hours and to normal levels within twenty four hours On the other hand, water soluble K analogs were not consistently active in reducing the prothrombin time[17] Similarly, Dam *et al*[18] have recently reported that preparations of the menadione group are practically valueless in dicumarol overdosage, but a single dose of 5 to 20 mg of K_1 given intravenously is effective within one or two hours, and it is effective within six hours when given orally However, there appears to be no marked difference between vitamin K_1 and "synkavite" in newborn infants when both are given either orally or intravenously[19] The synthetic vitamin K analogs are therefore recommended in hemorrhagic disease of the newborn and in pre-operative preparation of patients The availability of the synthetic vitamin K water-soluble analogs and the relatively limited availability of vitamin K_1 has probably been responsible for the more general use of the former[20]

Deficiency of vitamin K results in reduction of plasma prothrombin activity (true prothrombin and factor VII) The coagulation time of the blood is correspondingly prolonged and serious hemorrhages may occur Dam[1,2] showed that vitamin K deficiency results in the lack of more than one coagulation factor

Newborn infants commonly have plasma prothrombin concentrations which are 20 to 70 per cent of the adult level at birth[23] This value often decreases to as low as 20 per cent in the second and third days of life The coagulation factors spontaneously return toward normal adult concentrations in subsequent weeks[4] Vitamin K given to apparently normal infants at birth is effective in raising the prothrombin concentrations When plasma prothrombin concentration in the newborn falls to very low levels, a serious condition commonly referred to as "hemorrhagic disease of the newborn" may appear Vitamin K administered both intramuscularly and via stomach tube to infants in such a hemorrhagic state and whose prothrombin was less than 1 per cent of normal results in complete recovery of the blood prothrombin within forty-eight hours[5]

Webster and Fitzgerald[26] reported that the incidence of hemorrhagic signs in infants born to mothers not given vitamin K was about 10 times higher (1 18 per cent) than the incidence among infants from treated mothers (0 11 per cent)

Potter[27] compared the mortality rates of 6,004 infants whose mothers had received 3 2 mg of 2-methyl, 1-4 naphthoquinone-3-sodium sulfonate (water-soluble derivative of menadione) parenterally on admission to the labor rooms with 6,630 mothers who had not received any The mortality rates of the infants were the same In each series 1 infant died of possible hemorrhagic disease More recently in a study of over 10,000 infants born to mothers given vitamin K and over 20,000 not given the vitamin, the incidence of some form of hemorrhage in the newborn per 10,000 cases was 274 in the treated group and 363 in the untreated group[8] Dam and Plum[3] found that vitamin K given to mothers immediately before or during labor did not cause any important increase of prothrombin activity in non-asphyctic infants at birth However, a greater influence on prothrombin activity was found in asphyctic infants Routine prophylactic administration of vitamin K to mothers prior to delivery is generally recommended[4]

During prolonged antibiotic therapy, a vitamin K deficiency (produced by the suppression of vitamin K producing bacteria) may be responsible for some of the bleeding and hemorrhages that occur[29,30] Abnormal states of the intestinal tract, such as severe diarrhea may result in a lowered plasma prothrombin level[31] When bile is excluded from the intestine, as in obstructive jaundice absorption of the vitamin may be seriously impaired Surgical procedures in such cases may result in death from uncontrollable bleeding The plasma prothrombin concentration may be restored to normal by giving bile salts alone or bile salts with vitamin K by mouth It may be raised more rapidly by injecting vitamin K intramuscularly Improvement can sometimes be produced within a few hours by intravenous injection of a water-soluble vitamin K analog[17] although the results are not consistent[17,30]

When the liver is severely damaged, as by hepatitis, cirrhosis, or malignant disease, the prothrombin concentration of the blood may be lowered but in such cases administration of vitamin K by any route may not produce a rise. This lack of prothrombin response has been used as a test of liver function.[32]

Dicumarol which is 3,3′-methylene-bis-(4 hydroxycoumarin) acts as an anti metabolite for vitamin K. Because of its chemical resemblance,[33] it may replace vitamin K at the latter's normal site of action in the liver and thus prevent the vitamin from carrying out its normal function, or it may displace vitamin K from an enzyme system.[1] There is some evidence that vitamin K_1 Dicumarol antagonism is not a simple metabolite anti metabolite relationship.[34] Dicumarol does not disturb other functions of the liver. Thus Dicumarol acts as an anticoagulant by interfering with the synthesis of prothrombin. It has been used clinically in the treatment of phlebitis and coronary thrombosis.

Vitamin K is of no value in the treatment of hemorrhagic conditions that are not specifically due to a deficiency of prothrombin or which do not arise from an inadequate supply or utilization of vitamin K.

Large doses of vitamin K do not cause the prothrombin to rise above normal.[35–38] However excessive doses of the easily available substitutes, 2 methyl 1,4-naphthoquinone and the 2 methyl 1,4 naphthohydroquinone may produce toxic symptoms. When larger than necessary parenteral doses of water soluble vitamin K analogues are given to newborn infants there results increased bilirubinemia and an increase in incidence of kernicterus especially in premature infants who have erythroblastosis.[39] Thus in one report a sudden rise in kernicterus with six deaths resulted when the dose was increased from 10 mg once a day to 10 mg three times a day for three days.[40] The mechanism of action by which excess doses of vitamin K analogues produce hyperbilirubinemia is not understood. Most believe that an increase in hemolysis is involved but others consider the possibility of hepatocellular toxicity. Small doses are equally effective in preventing and in treating hemorrhagic disease resulting from hypoprothrombinemia and at the same time are not associated with undesirable effects. Therefore the Council on Drugs of the American Medical Association has recommended single doses of the water soluble analogues equivalent to 1 mg of synthetic vitamin K for prophylaxis and treatment of hemorrhagic disease of the newborn.[41] The Food and Nutrition Board of the National Research Council[42] concluded that synthetic water soluble K may be given to mothers in labor in dosages of 2 to 5 mg and to the newborn in dosages of 1 to 2 mg. There is probably no reason to fear harm from doses up to 5 mg especially in full term infants.[43] One report indicates that vitamin K itself, being a menadione derivative with a longer side chain in contrast to menadione and its water soluble derivatives causes practically no damage to red blood cells even after intravenous injection.[44] Nausea and vomiting result when as much as 3 mg of menadione per kg of body weight are given. Porphyrinuria was observed when 180 mg was given orally to humans.[45] When accidentally inhaled menadione is irritating to the respiratory tract. Severe dermatitis occurs frequently when the pure drug comes in contact with skin. In alcoholic solution it has vesicant properties

Recently another activity has been described Vitamin K and chlortetracycline (as well as vitamin E) have in common in their chemical structures the possibility of their participation in oxidation reduction reactions Vitamin K was found to reduce the number of *coliform bacteria* in the intestine of the rat and was conducive to the growth of yeast[46] Chicks given diets with added menadione or menadione bisulfate were more resistant to fowl typhoid[47–49]

Other observations indicate that vitamin K may be active in stimulating oxidative phosphorylation in tissues[50–53]

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VITAMIN E

By Harry H Gordon and Harold M Nitowsky

Introduction —In 1922–24 a specific dietary fat soluble factor, subsequently termed vitamin E was reported necessary for reproduction in the rat[1,2,3] Identified as an alcohol it was given the name tocopherol (tokos-childbirth, phero-to bring) Failure to establish a protective role for vitamin E in human reproduction discouraged critical clinical interest, but the importance of tocopherol to the health of both laboratory and domestic animals has led to productive studies of its mechanism of action and to gradual recognition of an emerging role in human nutrition

Chemistry —Pure vitamin E was first isolated from the unsaponifiable fraction of wheat germ oil in 1936[4] and its chemical structure[5] and synthesis[6] were reported in 1938 Tocopherol exists in natural sources as a series of closely related compounds, which differ in the number and position of the methyl groups attached to a chromane nucleus with a phytol side chain Vegetable oils, which are the richest natural source of tocopherols, contain different forms of vitamin E The tocopherols in corn oil are largely gamma tocopherol (7 8 dimethyl tocol) those in cottonseed oil are alpha (5 7 8 trimethyl tocol) and gamma tocopherols in about equal amounts those in soy bean oil are alpha gamma and delta (8 methyl tocol) forms and those in wheat germ oil are alpha and beta (5 8 dimethyl tocol) tocopherols Epsilon (5 methyl tocol) and zeta (5 7 dimethyl tocol) have been isolated from bran and barley oils respectively[7,8]

The various forms of vitamin E are the principal antioxidant components of natural fats they exert a protective action in inhibiting the oxidation of unsaturated fatty acids as well as other oxygen sensitive substances such as vitamins A and C Since their antioxidant activity depends on the presence of free phenolic groups, tocopherol esters are inactive until they are hydrolyzed

The differences in number and position of the methyl groups of the various forms of tocopherol affect their biological activity, and *in vitro* anti-

oxidant power Thus some of the tocopherols mentioned may be arranged in the order alpha > beta > gamma > delta according to biological activity and in reverse order according to antioxidant potency The apparent disparity between biological activity and antioxidant power may be explained in part by differences in the ease of transfer into animal tissues

The bivalent oxidation of alpha-tocopherol has been shown to yield two products that can be isolated, alpha tocopherylquinone and alpha tocopheroxide [9] The latter is active, but less potent than alpha-tocopherol, in restoring the fertility of rats on E deficient diets whereas alpha tocopherylquinone and its reduction product alpha tocopherylhydroquinone are inactive even in high doses [10, 11] In contrast nutritional muscular dystrophy induced in the rat and rabbit by vitamin E deficiency, can be prevented or cured by alpha-tocopherylquinone alpha-tocopherylhydroquinone or alpha tocopheroxide as well as by alpha tocopherol [1, 13]

Knowledge of the chemistry of alpha-tocopherol and its oxidation products is still far from complete Similarly, the metabolic fate of tocopherol in man is largely unkown although two new conjugated urinary metabolites have been described following the ingestion of large quantities of vitamin E [14]

Mechanism of Action —Numerous studies have been made of the effects of vitamin E deficiency in various animals as well as of the effects of the addition *in vitro* to various tissues and cell free systems However, a unifying concept is still lacking as to the mechanism of its action in the living organism

Since the tocopherols function as reversible antioxidants [15] it has been proposed that the primary biological role of vitamin E is as a physiological antioxidant *in vivo*, particularly in inhibiting the oxidation of unsaturated fatty acids in tissues Support for this contention comes from observations that certain signs of vitamin E deficiency in experimental animals such as exudative diathesis and encephalomalacia in chicks, occur only when unsaturated fatty acids are added to the vitamin E deficient diet Under such circumstances, lipoperoxides can be detected in the body fat at about the same time that disease appears The lipoperoxides are frequently associated with the development of a yellow-brown pigment part of which resembles the pigment ceroid by virtue of its acid fast staining properties with fuchsin Also favoring the physiological antioxidant concept is the fact that some antioxidants and redox substances unrelated to vitamin E such as methylene blue and diphenyl-p-phenylenediamine, afford partial or complete protection against certain manifestations of vitamin E deficiency These substances may act by exerting a sparing effect on small residual quantities of dietary or tissue stores of tocopherol[16] or they may act as antioxidants in situations where tocopherol does the same A possible *in vitro* model for an *in vivo* antioxidant action was suggested by the demonstration that alpha tocopherol and other phenolic antioxidants inhibit the hematin compound catalysis of unsaturated fatty acid oxidation and Vitamin A and carotene cooxidation [17] and also protect against *in vitro* hemolysis by H_2O_2 of red cells of tocopherol deficient rats and humans [18] These findings suggested the hypothesis that vitamin E may play a role in maintaining the integrity of the erythrocyte *in vivo* by inhibition of

oxidase action of hemoglobin on the unsaturated fatty acids of the cell membrane.[19]

The role of vitamin E as a physiologic antioxidant need not preclude a more specific action through some enzyme system. Recent studies strongly implicate tocopherol as one of the active components of the terminal respiratory chain in mammalian skeletal and heart muscle.[20] It appears to function as a cofactor in the cytochrome C reductase portion of both the DPN oxidase and succinate oxidase systems. Evidence for this role stems from the findings that:

a. tocopherol is present in rat skeletal muscle and bovine heart muscle preparations in amounts commensurate with those of other established cofactors;

b. isooctane extraction or aging, accompanied by freezing and thawing, inactivates cytochrome C reductase with a concomitant loss or dissociation of vitamin E from the enzyme; and

c. enzymatic activity is specifically restored by the tocopherol.

Whether tocopherol serves as an electron carrier undergoing reversible oxidation-reduction or merely as a binding material in this system has not been determined.

A role for vitamin E in other enzyme systems has been suggested from other evidence. Vitamin E deficient rabbits excrete extra quantities of allantoin,[21] have greatly increased liver xanthine oxidase activities[22] and show greatly increased incorporation of formate into the purines of both ribonucleic and desoxyribonucleic acids of skeletal muscle and marrow.[23] These findings suggest that vitamin E may control the exchange of the carbon of the 2 position of the purine ring, possibly through an effect on the synthesis or activity of coenzymes derived from folic acid.

Pathologic Findings in Animals.[24–28]—The absence of vitamin E from the diet has produced a variety of pathologic states, their nature and intensity depending on species, age or other constituents of the diet.

Reproductive failure associated with fetal resorption has been reported for the rat, mouse, hamster and guinea pig. In rats otherwise well nourished, vitamin E deficiency apparently does not interfere with ovulation, fertilization or implantation; death of the fetus and resorption result, however, from faulty development of the placenta. With lesser degrees of E depletion, fetuses may be born dead with thromboses of blood vessels and hemorrhages, and with still less E deficiency, animals may survive to develop late-lactation paralysis. Congenital malformations of umbilicus and skeleton have been reported for offspring of both rats and guinea pigs.

Testicular degeneration involving seminiferous tubules in many instances with accumulation of acid fast pigment in both germ cells and interstitial macrophages has been reported in varying degrees in monkey, dog, rat, mouse, hamster, rabbit, guinea pig, pig, chick and guppy fish. There is considerable variation in degree of degeneration in different species, *e.g.*, the testes of the Florida cotton rat and the mouse are particularly resistant to E deficiency.

Nutritional muscular dystrophy appears in a great number of species.[8] It was originally produced by dietary means in 1931,[29] but not established conclusively as due to lack of vitamin E until 1939.[30] It occurs as an acute,

explosive process in young animals, the prototype being the "late lactation" paralysis of rats or as a chronic dystrophy in older animals The following have shown one or both forms of the disease monkey, dog, rat, mouse hamster, cotton rat mink rabbit, guinea pig, sheep, goat, cattle, horse pig, chick, duck turkey pheasant, guppy fish Affected muscles are pale and gritty and show in varying degree interstitial edema, leukocytic infiltration fragmentation of muscle fibers, with loss of striation, nuclear breakdown hyaline necrosis and calcification, fibrosis, deposition of acid fast pigment and proliferation of sarcolemma nuclei If a prolonged E deficiency can be maintained adipose and connective tissue will replace the muscle fibers

In addition to the variations in intensity of the dystrophy in different animals and in the same animals at different ages the following points are of interest

1 Excessive creatinuria may precede the onset of clinical symptoms and its reversal by administration of vitamin E is excellent evidence of the relation to vitamin E [30]

2 Young rats born to mothers on diets deficient in vitamin E will while still suckling develop acute explosive, usually fatal "late lactation" dystrophy With no change in diet some will recover spontaneously and if kept on an E deficient diet ultimately develop chronic "adult" dystrophy [31]

3 Lesions of adult dystrophy which are spotty can be made more widespread by combining the dietary deficiency of E with deficiency of pyridoxine protein, or vitamin A Ascorbic acid and thiamine deficiency do not have this synergistic effect [31]

4 Exercise of limbs of rabbits on E deficient diets makes lesions more extensive and severance of the sciatic nerve or Achilles tendon prevents development of the lesions in the muscles on the operated side [3, 32]

Cardiac muscle also may show focal necrosis and fibrosis In herbivorous animals both laboratory and domestic, the lesion may develop rapidly to death in heart failure with virtually no previous symptoms In the rat hamster and cotton rat, on the other hand, extensive scarring with accumulation of acid-fast pigment in both muscle fibers and macrophages develops slowly Obvious clinical symptoms may be absent for months although electrocardiographic changes are present

Smooth muscle of the uterus, fallopian tube, vagina, small intestine, bronchi splenic capsule and trabeculae, prostate, seminal vesicle, vas deferens ureter, urinary and gall bladders, and blood vessels may develop deposits of acid-fast pigment granules both in the muscle fibers and in interstitial macrophages The accumulation of pigment differs in distribution in different species and is not seen in herbivorous animals or birds The pigment is apparently the same as the "ceroid" observed in rats who develop cirrhosis of the liver on low protein diets In mouse, rat hamster, pig and mink E deficiency leads to a spotty brownish discoloration of the fat due to accumulation of ceroid pigment In monkeys ingestion of unsaturated fatty acids is apparently required for its formation, this supports the concept that its accumulation is dependent on a decrease in biologic antioxidants

Subcutaneous collections of edema fluid, at times greenish because of

decomposed hemoglobin and gross edema and focal necrosis also at times greenish, in the brain, are vascular manifestations of E deficiency in chickens Embryonic death in chick eggs is associated with degeneration of blastodermic vessels and hemorrhage Hemorrhages have also been noted in the E deficient rat fetus and in the cranial and visceral cavities of puppies born to E deficient dogs

Although tocopherol deficiency cannot alter the fatty infiltration and fibrosis of nutritional cirrhosis of the liver due to choline or methionine deficiency, it does permit the development of ceroid pigment in the liver Furthermore vitamin E deficiency when combined with deficiency of sulfhydryl containing amino acids and of selenium (Factor 3 of Schwarz) permits development of acute hemorrhagic necrosis of the liver The extent to which the various manifestations of vitamin E deficiency are altered by the amounts of selenium in the diet is now the subject of lively investigation[34–36] Depigmentation of dental enamel in the rat renal tubular degeneration, increased hemolysis of the erythrocytes of rats in dialuric acid or in dilute hydrogen peroxide, and of humans in dilute hydrogen peroxide and loss of subcutaneous fat in the rat and mouse have all been noted in vitamin E deficiency The administration of large doses of vitamin K to E *deficient rats produces intravascular hemolysis* [37] *Anemia and granulocytosis* have been reported in E deficient monkeys [8]

Role in Human Nutrition — The wide variety of pathologic conditions seen in animals has led to numerous therapeutic clinical trials but prompt explosion of extravagant claims of benefit as in for example pseudohypertrophic muscular dystrophy habitual abortion and coronary heart disease has discouraged critical clinical interest More recently evidence has accumulated which may ultimately define the role of vitamin E in human nutrition

In patients with absorptive defects low plasma tocopherol levels have been reported[39] as well as deposition of ceroid pigment [40] A peculiar lesion of muscle was reported in 1908 in a patient with sprue [41] In patients with cystic fibrosis of the pancreas who have steatorrhea increased hemolysis of erythrocytes in hydrogen peroxide and low concentrations of plasma tocopherol have been found [4, 43] Furthermore many of these patients have had an excessive creatinuria while on a creatine-poor diet and this has decreased when tocopherol was administered orally [44] Lesions in the muscle similar to those produced in animals on E deficient diets have been reported in association with evidence of deficiency of vitamins A and D in a child who died with cystic fibrosis of the pancreas [4] The failure to make extensive examinations of muscles routinely at post mortem and the existence of other possible etiologic factors[46] complicate judgment of the significance of this finding, but the report of ceroid in the intestinal wall of patients with cystic fibrosis of the pancreas[47] confirms the biochemical indications that patients with cystic fibrosis of the pancreas do in fact have a proven deficiency of vitamin E

Patients with congenital biliary atresia also have tocopherol deficiency as evidenced by low plasma tocopherol increased hemolysis of erythrocytes and excessive creatinuria Raising the plasma tocopherol by administration of intravenous tocopherol esters did not decrease the creatinuria, but

in an adult with xanthomatous biliary cirrhosis administration of tocopheryl esters orally and parenterally increased plasma tocopherol and decreased pentosuria and creatinuria [48] Patients with kwashiorkor have been reported to have low plasma tocopherol and focal lesions in skeletal muscles [49]

Low plasma tocopherol and increased hemolysis of erythrocytes in dilute hydrogen peroxide have been reported for newborn infants, both full term and premature [50-53] The plasma tocopherol of full term infants rises promptly on feeding of breast milk and more slowly with feeding of cows milk [51] Prematurely born infants who are fed cows' milk mixtures from

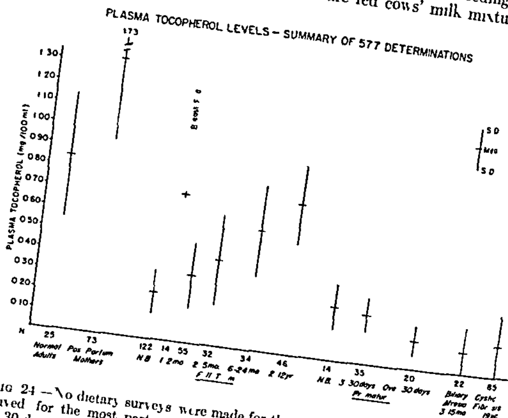


FIG 24 —No dietary surveys were made for these subjects The premature infants received for the most part, partially skimmed cows milk and some of the infants over 30 days of age received oral iron medication which oxidizes tocopherol The full term infants with the exception of one group on human milk as well as the subjects with cystic fibrosis of the pancreas and biliary atresia, received diets of cows milk plus varied solids (Gordon *et al* courtesy of Pediatrics, *21*, 673 1958)

which part of the cream has been removed have persistently low plasma tocopherol and increased erythrocyte hemolysis in hydrogen peroxide, and tocopherol supplementation of their diets has been recommended [54]

To date no clinical biochemical, physiologic or pathologic correlates have been noted for this physiologic deficiency in newborn infants Pregnant women have tocopherol levels considerably above the levels of non pregnant adults Tocopherol depletion for more than a year has been found necessary to lower the adult plasma tocopherol level from 1 to 0 5 mg/100 ml [55] A plateau of at least another 12 months at 0 5 mg was found during which body stores probably in liver and adipose tissue, yielded tocopherol to maintain the plasma concentration Since tocopherol and cholesterol

concentrations in the plasma vary directly in some conditions,[39] one must consider that transport factors as well as state of tocopherol nutrition determine the plasma concentration.

Tocopherol Content of Food[56,57]—The richest dietary sources are vegetable oils such as those obtained from corn, soya bean, peanut, coconut or cottonseed, with cereal products and eggs next in order. Other vegetables supply little of the daily intake because of their low concentration of total tocopherols and because of the small proportion as alpha tocopherol with its relatively greater biologic activity. Animal products have a low content of total tocopherol but a high proportion is the alpha form. The mean daily intakes of total and alpha tocopherol by adults in an American city have been estimated as 24 and 14 mg per day when calculated from figures for average food consumption. Human colostrum contains from 0.13 to 3.6 mg of total tocopherol per 100 ml; in human milk frozen within a week after collection, the values ranged from 0.10 to 0.48 mg/100 ml. The mean concentration of 0.24 mg/100 ml is approximately twice that of evaporated cows' milk diluted 1:1 with water.

VITAMIN E CONTENT OF THE AVERAGE DAILY PER CAPITA FOOD CONSUMPTION IN THE U.S. IN 1948 (U.S.D.A. 49)

Commodity	*Average Consumption*	*Vitamin E Intake*	
		total tocopherol	*a Tocopherol*
	gm/day	*mg/day*	*mg/day*
Fats and oil, incl. butter	80.8	14.42	7.87
Grain products	212.5	2.85	1.78
Meat, poultry and fish	196.4	1.17	0.99
Potatoes and sweet potatoes	142.9	0.87	0.84
Eggs	58.4	1.16	0.68
Dairy products, excl. butter	535.6	0.58	0.58
Green leafy and yellow vegetables	141.7	1.15	0.50
Dried peas, beans and nuts	19.9	1.23	0.43
Citrus fruits and tomatoes	130.5	0.38	0.35
Other vegetables and fruits	290.8	0.17	0.12
Coffee, tea and cocoa	23.6	0.13	0.06
Sugar and syrups	131.7	0.00	0.00
Totals	1,964.8	24.12	14.20 (59% of total tocopherols)

(Harris *et al.*, J. Nutrition *40*, 367, 1950.)

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THIAMINE, RIBOFLAVIN AND NIACIN

By M. K. Horwitt

Introduction

In 1882, Takaki,[1] the Director General of the Naval Medical Service in Japan, demonstrated that beriberi in the Japanese navy could be cured by decreasing the rice ration and increasing the use of barley, vegetables, meat and condensed milk. Though he received full recognition from his own government for this momentous achievement, Takaki's work did not carry conviction among European scientists. In 1897, Eijkman[2] published observations on "an illness of fowls similar to beriberi." The hens, eating leftovers from meals fed to inmates of a Netherlands East Indies prison where Eijkman was the physician, developed stiffness and weakness of the extremities very suggestive of beriberi patients. At that time, he postulated that the disease was due to a toxin in polished rice that could be neutralized by a substance present in rice polishings. In 1901, his associate, Dr. Grijns,[3] suggested that the disorder was due to a lack of something in polished rice, and the concept that this was a deficiency disease began to develop. However, it was not until after 1911, when Casimer Funk[4] coined the word "vitamine," and attracted public attention to the fact that there are antiscorbutic, antipellagric and antirachitic substances in addition to an antiberiberi factor, that the modern vitamin era began.

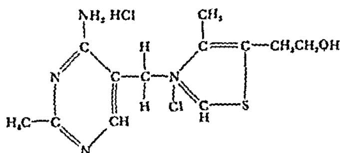
The food fraction termed "water soluble B" was reported by McCollum and Kennedy[5] in 1916 with the suggestion that it might be identical with the antiberiberi substance which was first shown to be dual in nature in 1920 by Emmett and Luros.[6] This was further studied by Smith and Hendrick[7] who in 1926, divided the complex into a beriberi preventative material which was destroyed by heat and an antipellagric substance which was more heat stable. About the same time Goldberger and Lillie[8] were making their classical demonstrations that pellagra could be cured by dietary means and the term "vitamin B_1" began to represent the water-soluble, heat-labile, antineuritic fraction, and vitamin B_2 or G, the heat-stable antipellagric fraction. Soon after Warburg and Christian[9] discovered the first flavoprotein in 1932, the close correlation between the vitamins and biological oxidations was recognized from the combined observations of Ellinger and Koschara,[10] Booher,[11] and Kuhn *et al.*[12] and riboflavin deficiency was proved responsible for some of the pathology formerly associated with pellagra.

It was not until 1937, when Elvehjem, Madden, Strong, and Woolley[13] demonstrated that nicotinic acid would cure the animal analogs of pellagra, that the direct correlation between human pellagra and nicotinic acid became apparent.[14–18] Recently, interpretations of the sparing effects of animal protein on nicotinic acid requirements have established the ability of the mammalian organism to convert tryptophan in the diet to nicotinic acid.[19]

Thiamine

The Discovery and Chemical Nature of Thiamine.—The first attempts to isolate or concentrate the anti-beriberi factor were made in 1912 by Suzuki *et al.*,[20] Edie[21] and Funk[22] who used aqueous extracts of rice polish-

ings and yeast, as their source materials However, it was not until twelve years later that Jansen and Donath,[23] working in Java, effected a much greater concentration than the earlier workers[24] After absorbing the active material in alcohol extracts from rice polishings on fuller's earth, precipitating with silver nitrate, and finally forming a platinic chloride complex, they were able to isolate and crystallize thiamine hydrochloride The dedication of R R Williams to the eradication of beriberi, has provided a fascinating story of successful achievements in the alleviation of this scourge of mankind While working in the capacity of chief chemist of the Philippine Bureau of Science 1909–1916, he brought about a marked reduction in infantile beriberi in that section of the Orient by using extracts from rice polishings Vedder and Williams[25] confirmed Funk's earlier observation that the anti-neuritic properties were associated with a pyrimidine-like structure Once aware that Jansen and Donath's crystals showed remarkable curative properties in the treatment of the deficiency in rats, many investigators[26-29] became engaged in attempts to synthesize thiamine The brilliant series of investigations carried out by Williams and his collaborators,[30] produced a compound with the following structure



Thiamine Hydrochloride

2 methyl 5 (4 methyl 5 β hydroxyethyl thiazolium chloride) methyl 6 aminopyrimidine hydrochloride

Thiamine hydrochloride is a white crystalline substance Although it usually has a characteristic odor and taste which has been described as nutlike and yeasty ' it is said to be odorless when pure It is soluble in water (1 gm per ml) less soluble in 95 per cent ethyl alcohol (1 gm per 100 ml) and insoluble in ether, acetone, chloroform and benzene Thiamine is rapidly destroyed in neutral or alkaline solution into its constituent pyrimidine and thiazole compounds, but is stable in the dry state In acid solution it can be stored for some time without loss of activity Gastric juice has little or no effect on this vitamin,[31] but bile and duodenal pancreatic juice, which are slightly alkaline, rapidly destroy thiamine There is a linear relationship between the reaction velocity of the destruction of thiamine and the hydrogen ion concentration of any given buffer[3] in the pH range of 3 to 8 It has also been shown that copper catalyzes the destruction of thiamine but iron, aluminum, zinc and tin had no effect[33]

There is an enzyme in raw carp[34] and raw herring[35] called thiaminase which can cause a rather rapid destruction of thiamine activity when the raw fish is mixed with a diet The disorder called Chastek paralysis in

foxes has been reproduced by feeding 10 per cent or more of fresh whole fish in the diet[36] According to Krampitz and Woolley,[37] the enzyme causes a hydrolytic cleavage of the thiamine molecule into the thiazole and pyrimidine halves

Estimation of Thiamine —Most of the early thiamine assays were based upon the controlled production and cure of polyneuritic symptoms in pigeons[38, 39] in which the recovery from symptoms brought about by feeding an unknown was compared with that obtained from a standard preparation[40] Later studies on rats[41–43] and chicks[44] as test animals improved the sensitivity of the tests so that differences of as little as one microgram of the active substance became detectable

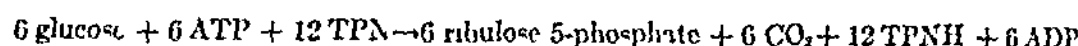
After the introduction of crystalline thiamine, it was noted by Jansen[45] that when thiamine reacts with alkaline potassium ferricyanide, thiochrome was formed Thiochrome which is a fluorescent substance can be extracted with isobutyl alcohol and measured in a fluorimeter This reaction has been quantitated by Hennessey and Cerecedo[46] and Connor and Straub[4] and has been generally recognized as the accepted procedure for the analysis of thiamine in animal and plant products

Physiological Function of Thiamine —In 1935, Thompson and Johnson[48] showed that pyruvate accumulates in the blood of animals in experimental vitamin B deficiency Previously, Kinnersley and Peters[49] had shown that the brain of the deficient pigeons contained increased amounts of lactic acid When, in 1936, Peters[50] reported on the direct relationship between thiamine deficiency and the accumulation of lactic and pyruvic acid in pigeon brain slices in glucose substrate the door was opened to fundamental investigations on the function of thiamine In 1937 Lohman and Schuster[51] found that thiamine diphosphate acts as a coenzyme to carboxylase an enzyme which catalyzed the decarboxylation of pyruvic acid to acetaldehyde and carbon dioxide Since then it has been ascertained that this cocarboxylase is capable of catalyzing other reactions[5] although the prime function of thiamine appears to be its role in pyruvate metabolism

Most of the cocarboxylases are thiamine pyrophosphate-magnesium-protein compounds[5-a] Thiamine pyrophosphate cannot be replaced by *thiamine or monophosphothiamine in pure preparations that do not con*tain a phosphorylating system Accordingly the only enzyme known to effect thiamine in animal tissues is that which promotes the reaction between thiamine and adenosinetriphosphate to form cocarboxylase and adenylic acid This enzyme has been isolated and partially purified from intestinal *mucosa* *Thiamine* triphosphate has an activity that is similar to that of thiamine pyrophosphate but is much less active

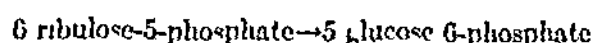
Thiamine pyrophosphate is known to participate in at least three reactions in intermediary mammalian metabolism which have been summarized by Handler[55] It is necessary for the opening step of the reactions which feed into the citric acid cycle where pyruvic acid is decarboxylated and "active acetaldehyde" is combined with thiamine before it is transferred to the oxidized form of lipoic acid The lipoic acid is thereby reduced and acetyl lipoic acid is formed The second reaction is the oxidative decarboxylation of *α* ketoglutaric acid which comes later in the citric acid cycle Here, similar to that described for pyruvic acid decarboxylation, the

α-ketoglutaric acid is decarboxylated and "active" succinyl semi-aldehyde exists transiently on the thiamine before being transferred to lipoic acid to form succinyl lipoic acid from which the succinyl group is transferred to coenzyme A. The third reaction is the transketolase reaction in which thiamine pyrophosphate is the coenzyme necessary to catalyze products formed in the direct oxidative pathway of glucose metabolism which apparently occurs in all tissues except skeletal muscle. The combined reactions involved are represented by the equation



$$6 \text{ glucose} + 6 \text{ ATP} + 12 \text{ TPN} \rightarrow 6 \text{ ribulose 5-phosphate} + 6 \text{ CO}_2 + 12 \text{ TPNH} + 6 \text{ ADP}$$

Thus one glucose molecule is completely oxidized to form 12 TPNH. The remainder of the process is represented by the equation



$$6 \text{ ribulose-5-phosphate} \rightarrow 5 \text{ glucose 6-phosphate}$$

These are general reactions for other ketopentoses in addition to ribulose.

Attempts to explain the symptoms of beri beri from our knowledge of cellular biochemistry have not been fruitful. Until better information is forthcoming one must assume that some product, like pyruvate, may, in the absence of adequate thiamine, accumulate to produce abnormal effects.

Nature of Thiamine Deficiency.—*Classical beriberi, which has been* known for centuries in oriental countries is rarely seen in Europe and the United States except in alcoholism under conditions where negligible amounts of thiamine are consumed. The disorder is characterized by degenerative changes in the nervous system which first involve the lower extremities and develop into a multiple peripheral neuritis. This may or may not be accompanied by edema with subsequent cardiac hypertrophy and dilatation. Clinical beriberi is apt to be a mixed deficiency[3] with co-existing deficiencies in other vitamins. It is a disease which, although associated with a long-standing deficiency of thiamine is properly regarded as a multiple deficiency syndrome which does not occur if an adequate supply of thiamine is utilized. Beriberi in adults[53a] and older children may be of three main types: (a) the chronic, dry atrophic variety chiefly characterized by multiple peripheral neuritis, generally found only in older adults, (b) the mild and sub-acute forms in which the neurological manifestations may include alterations in tendon reflexes and in which paresthesias, edema and muscle cramps are common, (c) the acute fulminating type in which cardiac failure is a prominent feature. The amount of edema found in acute beriberi may vary and may not be related to the severity of the symptoms. Studies on experimentally produced thiamine deficiencies in man[54,55] have shown that soon after evidence of increased amounts of lactate and pyruvate are noted in the blood one hour after glucose ingestion, symptoms of loss of appetite, nausea and depressed *tendon and Achilles reflexes developed. The pronounced polyneuropathy* was accompanied by tenderness of the calf muscles and diminished vibration sense. The recovery from these symptoms is dramatic.[55] Soon after thiamine is provided, the nausea disappears and the appetite returns within a few hours. Of interest, is the observation that bed rest and fasting are ameliorative during the early stages of thiamine deficiency. This is consistent with the theoretical observations that thiamine is necessary for

the utilization of carbohydrate, that exercise causes a demand on carbohydrate turnover[56] and that fat utilization does not require thiamine[57] and may indeed be sparing of thiamine

Recognition and Etiology of Thiamine Deficiency —In controlled thiamine deficiency[54 55] states on dietary levels of 0 2 mg per day one does not note any clinical signs of deterioration until after the urinary excretion has dropped to levels of less than 50 micrograms of thiamine per day [5 58] This is followed by the biochemical lesion in carbohydrate metabolism which is manifested by elevations in the blood levels of lactic and pyruvic acids after glucose ingestion and/or glycogen utilization (exercise) During these early changes there are no easily demonstrable alterations in the basal levels of lactate or pyruvate [56] At about the same time (after two to three months on the deficient diet) one notes a loss of appetite, which may be associated with the discomfort of elevated pyruvate levels at mealtime The neurological and cardiovascular signs develop quite slowly, in the subsequent three months at which time the thiamine excreted in the urine is less than 25 micrograms per day

Since the deficient organism excretes thiamine less readily, it is axiomatic that if thiamine in amounts of 100 mcg a day, or more is found in the urine the diet is not deficient in thiamine This does not imply that excretion levels lower than 100 mcg per day signify thiamine deficiency

An adequate diet given to individuals who have pathology as a consequence of thiamine-lack, causes a very prompt repair in the biochemical lesions involved, but the neurologic signs may be slower to repair Among the clinical symptoms which may remain for some months after thiamine supplementation are the diminished patellar and Achilles tendon reflexes According to Jolliffe [53] peripheral neuropathy that does not involve the lower extremities and is not bilateral and symmetrical is not due to thiamine deficiency alone Wernicke's disease,[59] which occurs most often in association with chronic alcoholism is usually a multiple deficiency This disorder is characterized by ophthalmoplegia, polyneuropathy ataxia and progressive clouding of the consciousness The ophthalmoplegia is relieved by thiamine administration in from forty-eight to ninety-six hours Cardiac forms of beriberi respond favorably to thiamine therapy [60]

Thiamine Requirements of Man —Although fat, protein and alcohol[61 6] exert thiamine sparing activities, for practical purposes it seems best to continue to consider the thiamine requirements in terms of total calories in the diet Studies of thiamine requirements of adults by Elsom [63] Williams[64] and Oldham,[64] and their associates indicate that the minimum requirement for thiamine is between 0 35 and 0 5 mg per 1000 calories Other investigators[55 65 66] have reported the minimum requirement to be 0 23 mg or less for each 1000 calories

The present recommended allowance of the Food and Nutrition Board of the National Research Council is 0 5 mg per 1000 calories for energy need of less than 3000 calories For each additional 1000 calories needed above the 3000 calorie level 0 2 mg of thiamine are added Less than 1 mg of thiamine a day is not recommended for adults even though the caloric consumption be below 2000 calories

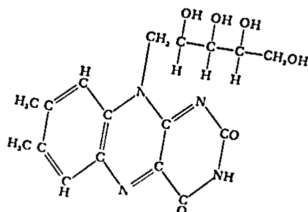
The thiamine requirements of infants have been estimated by Holt and

associates[67] as being between 0 14 and 0 20 mg per day It appears that the minimum requirement for the infant in relation to calories is similar to that of the adult and one assumes that the same values would prevail for various ages of childhood, adolescence and old age[68]

Food Sources —The richest sources of thiamine are pork, liver, yeast, whole cereals and fresh green vegetables Among the poorer sources are non-enriched flour, rice, and processed cereals Human milk is a relatively poor source of thiamine, containing about 20 mcg per 100 ml[69] Many foodstuffs lose considerable thiamine during cooking and serving While there is little inactivation in foods heated in acid or neutral solutions at 100° C, higher temperatures and increased alkalinity hasten the rate of destruction Freezing causes little or no loss in the thiamine content of foods

Riboflavin

The Isolation and Chemical Nature —Although the water soluble, yellow-green fluorescent compound in whey was known to chemists in the 19th century,[70] the recognition of the biological importance of this substance did not come until after Warburg and Christian[9] discovered the first flavoprotein in 1932 This was followed almost immediately by the isolation of riboflavin by Kuhn, Gyorgy and Wagner-Jauregg[12] and the recognition of its B_2 growth-promoting properties by Booher[11] The synthesis of riboflavin was accomplished by Kuhn[71] and Karrer[72] and associates in 1935 who showed that the compound was 6 7-dimethyl 9 (d1'ribityl) isoalloxazine



Riboflavin

6 7 dimethyl 9 (D 1 ribityl) isoalloxazine

The methods of isolation varied somewhat with the source of the material but nearly all the early workers used adsorption on fuller's earth for slightly acid extracts The resulting adsorbate was extracted with pyridine solutions, or dilute ammonia and the eluate, after concentration, was precipitated with a heavy metal to form a salt of flavine Until it was recognized that all were dealing with the same substance, the pigments were given specific names like ovoflavin, lactoflavin, hepatoflavin, and uroflavin

Riboflavin crystallizes in yellowish brown needles Solubility is relatively slight, being only 12 mg per 100 ml at 27 5° C Riboflavin-5 phosphate, the flavin mononucleotide, is much more soluble Both riboflavin and its phosphate are decomposed by exposure to light and in strongly alkaline solutions The typical fluorescence of riboflavin is dependent upon the presence of a free 3 imino group, and neither 3 substituted riboflavin nor the enzyme systems will fluoresce

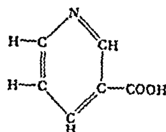
The Estimation of Riboflavin —Although the growth of rats[73] and chicks[74] may occasionally be used to assay riboflavin in mixed diets the biological method of assay has been generally superseded by the microbiological method of Snell and Strong[7] This measures the lactic acid production of a lactic acid producing organism which is dependent upon the presence of riboflavin in the medium

The chemical assay of riboflavin relies upon the fact that the fluorescence of riboflavin is proportional to its concentration under controlled conditions of salt concentration pH and temperature Interfering substances may be removed by *potassium permanganate*[76] *or by adsorption on* Florisil[77]

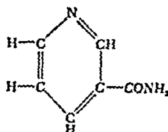
Physiological Functions of Riboflavin —Knowledge of the close relationship between the vitamins and biological oxidations may be said to date from 1932 the year in which the first flavoprotein was discovered This compound, often referred to as the ' old yellow enzyme was soon separated into a protein and a yellow prosthetic group[9] Stern and Holiday[78] found that the prosthetic group of Warburg s yellow enzyme was a derivative of alloxazine This fact, when combined with the observations of correlations between vitamin B requirements and concentration of the yellow green fluorescence was soon corroborated by the synthesis of riboflavin Theorell's[79] demonstration that Warburg s enzyme contained one molecule of phosphate and the proof of constitution of riboflavin 5 phosphate were the concluding steps in the first separation, identification and synthesis of the prosthetic group of an enzyme

Mammalian tissues have been shown to have a number of different flavoprotein enzyme systems each containing a specific protein (apo enzyme) and a riboflavin-containing prosthetic group (co enzyme) These enzymes are important components of the oxidative systems in living cells and it is axiomatic that cellular growth cannot evolve in the absence of riboflavin During periods of riboflavin deficiency negligible amounts of riboflavin are excreted in the urine and one might surmise that the body is capable of utilizing much of the riboflavin released by its own catabolic processes However the day by day needs of this vitamin for tissue turn over in the adult appear to be greater than 0 5 mg per day, and the decomposition products of riboflavin must be excreted in forms not recognized at present

It is reasonable that any local trauma to the skin must be repaired by new growth[80] Such trauma might range from erosions at the angles of the mouth an area that is constantly flexed or to surgical intervention The lesions formed are repaired by local growth only to the extent that riboflavin and protein is available In the absence of riboflavin, minor injuries



Nicotinic acid (Niacin)
pyridine 3 carboxylic acid



Nicotinamide (Nicotinic Acid Amide, Niacinamide)
pyridine 3 carboxylic acid amide

Niacin is β-pyridine carboxylic acid This is easily converted to the physiologically active nicotinic acid amide (niacinamide) Niacin is a nonhygroscopic, stable, white crystalline solid which sublimes without decomposition at about 230° C It is soluble in water (1 gm to 60 ml at 25° C) and in alcohol (1 gm in 80 ml at 25° C) and insoluble in ether Niacinamide is much more soluble in water (1 gm in 1 ml) and in alcohol (1 gm in 1 5 ml) and is also soluble in ether

The Estimation of Nicotinic Acid —Although animals have never been completely satisfactory subjects for the assay of the pellagra-preventive factor, dogs have been used to produce uncomplicated niacin deficiency [117,118] The chemical technique most often used depends upon the Konig reaction[119] in which the pyridine compound reacts with cyanogen bromide and an organic base to form a yellow color [120,121] In recent years the microbiological methods as illustrated by that of Snell and Wright[122] have been more popular This depends upon the amount of lactic acid produced by *L arabinosus* on a synthetic medium containing all known growth factors except niacin

The Biological Function of Nicotinic Acid —The physiological significance of nicotinic acid was understood in 1935 by Warburg and Christian[123] before its importance in nutrition was recognized Their isolation of co-enzyme II, a compound of adenine, nicotinamide, two molecules of ribose and three molecules of phosphoric acid was followed by the recognition that this co-enzyme, triphosphopyridine nucleotide (TPN) was a specific codehydrogenase for a series of dehydrogenases which included, among other enzymes, those involved in changing glucose-6 monophosphate to phosphogluconic acid, and citric acid to α-ketoglutaric acid Co-enzyme I (cozymase) or diphosphopyridine nucleotide (DPN) is similar in general action and in structure except that it contains two molecules of phosphoric acid It is a specific codehydrogenase for enzymes responsible for converting lactic acid to pyruvic acid, alcohol to acetaldehyde, β-hydroxybutyric to acetaldehyde, and for many other reactions

DPN and TPN serve as parts of the intracellular respiratory mechanism of all cells They assist in the stepwise transfer of hydrogen from a product of glycolysis to flavin mononucleotide which in turn with the help of specific enzymes, transfers this hydrogen to the cytochromes which in turn transfer the hydrogen to oxygen to form water [124]

Clinical Aspects of Nicotinic Acid Deficiency.—Although the disease, pellagra, has been endemic in corn-eating areas of the world for over two hundred years, it was not until about 1908 that the diagnostic symptoms of pellagra were clearly recognized.[125] Usually, the early symptoms are weakness, lassitude, anorexia and indigestion. This is followed by the classical "three D's," dermatitis, diarrhea and dementia.

The dermatitis has a characteristic appearance on those parts of the body exposed to sunlight, heat, or mild trauma. The lesions are distributed on the face, neck, and surfaces of the hands, feet, elbows and other parts of the body which may be subject to mechanical irritations or contact with body secretions. Usually the lesions of pellagra are bilaterally symmetrical. In a recent study by Goldsmith *et al.*[126] of experimentally produced pellagra, the importance of oral lesions as diagnostic signs were confirmed.

Although diarrhea is a prominent feature in the pellagric patient, it may not develop in all cases.[127] The diarrhea may be severe and may be accompanied by vomiting and a dysphagia, a mouth inflammation which may be so painful that the patient refuses food and becomes emaciated.

The mental symptoms develop in untreated cases.[128] Irritability, headaches, sleeplessness, loss of memory or other signs of emotional instability often accompany the early signs of pellagra. In advanced cases, a toxic confusional psychosis with symptoms of acute delirium and catatonia have been observed.

Lesions of the nervous system are nonspecific. Scattered degeneration of the axis cylinders of the pyramidal cells of the cortex and a myelin degeneration of fibers of the spinal column have been found.[129] Peripheral lesions are uncommon.

Recognition of the deficiency of dietary intake of nicotinic acid or tryptophan-containing proteins can be obtained by analyzing the urine for its N'-methylnicotinamide content. Whereas the normal daily excretion is usually over 3 mg., subjects on a restricted diet providing 4.7 mg. of niacin and 190 mg. of tryptophan for sixty days had excretions of approximately 0.5 mg. per day.[126] Slightly higher excretions of N'-methylnicotinamide were obtained in another study in which a diet providing 5.8 mg. niacin and 265 mg. of tryptophan daily were fed for more than a year.[130]

Nicotinic Acid Requirements of Man.—Dietary levels of less than 7.5 mg. a day have been associated with the production of pellagra[1,6,131,132] but it is not correct to speak about nicotinic acid needs without considering the amount of tryptophan in the diet. Not only can tryptophan alone heal the lesions of pellagra[133–135] but it may be more nearly correct to think of pellagra as a tryptophan deficiency since corn products are relatively more deficient in tryptophan than in nicotinic acid.[136,137]

The term niacin-equivalent[136] was introduced to facilitate the calculation of the combined effects of nicotinic acid and tryptophan in the diet. The amount of tryptophan chosen to be equivalent to 1 mg. of nicotinic acid was 60 mg. This ratio is a compromise based upon studies of the amounts of tryptophan converted to N'-methylnicotinamide and its metabolites in human subjects.[130,138] Obviously such a relationship can not be expected to

be inflexible under all conditions of genetic, physiological, and dietary variations but the fact that some protein foods, practically devoid of nicotinic acid can supply all the niacin-equivalents necessary for optimal health makes it practical to have some estimation of the amounts of tryptophan in the diet in order to evaluate nicotinic acid requirements This is illustrated in Table 26

TABLE 26 —NIACIN EQUIVALENTS OF REPRESENTATIVE FOODS

Food	Niacin	Tryptophan	Niacin Equivalent
	mg /1000 calories	mg /1000 calories	per 1000 calories
Cow's milk	1 21	673	12 4
Human milk	2 46	443	9 84
Beef, round	24 7	1280	46 0
Whole eggs	0 60	1150	10 8
Salt pork	1 15	61	2 17
Wheat flour	2 48	297	7 43
Corn grits	1 83	70	3 00
Corn	4 97	106	6 74

An interesting point that comes out of comparisons of old and new studies of human requirements is the calculation that the requirement for niacin-equivalents is dependent upon the total caloric intake either as a function of metabolism plus work or of body size Accordingly, it may be necessary to think of niacin-tryptophan requirements, as one does for thiamine requirements, as being related to calories consumed An illustration of this may be had from comparing the experimental pellagra producing diet used by Goldberger[139] with those used by Goldsmith et al,[1 8] and in the Elgin Studies [130] The Goldberger diet provided 6 7 mg nicotinamide and 330 mg tryptophan in 3000 calories or 4 1 niacin-equivalents per 1000 calories whereas diets in the other studies, which provided 5 2 mg of nicotinamide plus 235 mg tryptophan in 2000 calories or 4 4 niacin equivalents per 1000 calories, did not produce pellagra In the Tulane studies,[1 8] diets which provided less than 4 4 niacin-equivalents per 1000 calories even at levels of intake of 2000 calories did produce pellagra

To put the figure of 4 4 mg of niacin-equivalent per 1000 calories in proper perspective it should be compared with levels of intake of thiamine and riboflavin below which pathological symptoms appear This would be about 0 18 mg of thiamine per 1000 calories and about 0 6 mg of riboflavin per day Accordingly, the 1958 Recommended Dietary Allowances suggest a level of 6 6 niacin-equivalents per 1000 calories or 20 niacin equivalents for a 3000 calorie diet This amount would be provided easily by a regimen including 60 grams of mixed protein plus 10 mg of nicotinic acid For practical purposes endemic pellagra remains a disease associated with maize-eating populations

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PANTOTHENIC ACID

By Richard W Vilter

Introduction —Pantothenic acid, a white crystalline compound, isolated in 1938[1] and synthesized in 1940 proved to be identical with the chick anti-dermatitis factor and the liver filtrate factor for rats It is widely distributed in nature and has been found in all forms of living things The derivation of its name is based on this property

Distribution in Foods.—As is indicated in Table 27, liver, meat, cereal milk and many other foods are reliable sources. Bacteria synthesize it and the gastro-enteric tract organisms of animals and man probably provide a considerable amount to the host.

TABLE 27.—PANTOTHENIC ACID CONTENT OF FOODS
(Micrograms per gram of edible portion)

Meats	
Beef Kidney	40.64
Beef Liver	93.36
Beef Rib	5.42
Lamb Kidney	47.43
Lamb Liver	70.99
Lamb Leg	8.86
Pork Liver	70.08
Ham	6.94
Rabbit Liver	45.03
Rabbit Muscle	7.90
Eggs	
Whites	1.44
Yolk	42.35
Whole	15.76
Nuts	
Almonds	5.78
Cashews	11.62
Coconut Meat	1.93
Walnuts	9.70
Vegetables, Fresh	
Beans, green snap	2.02
Broccoli	12.87
Cabbage	2.80
Carrots	2.72
Corn, yellow	8.89
Eggplant	2.05
Kale	12.88
Lettuce	3.63
Onion	1.68
Potato, white	4.05
Spinach	3.12
Squash, zucchini	3.40
Sweet potato	9.35
Tomato	3.14

Vegetables, dried	
Cowpeas	12.43
Kidney beans	6.50
Lima beans	12.99
Navy beans	12.08
Lentils	14.99
Splitpeas	21.16
Fruits	
Avocado	11.35
Bananas	3.06
Oranges	2.21
Pineapple	1.75
Cereals	
Oats	12.13
Cornmeal	5.93
Rice, white	6.40
Wheat	10.95
Wheat bran	29.03
Yeast, brewers	99.24
Milk, Cheese	
Skim milk	3.75
Whole milk	3.23
Cottage Cheese	2.80

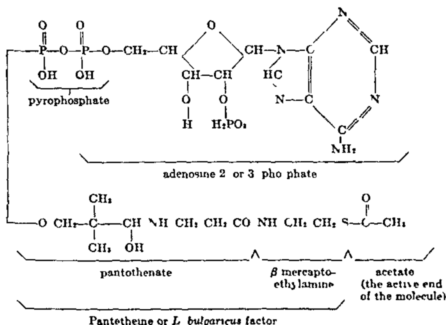
(From Agriculture Handbook No. 97, September 1956, United States Department of Agriculture.)

Biochemical Functions of Pantothenic Acid.—Pantothenic acid is made up of α,γ-dihydroxy β,β'dimethyl butyric acid and β alanine. Almost all of it exists in tissues in bound form. The synthetic vitamin is available as the calcium salt.

Pantothenic acid is a fundamental and essential part of a very important catalyst of acetylation reactions, called co-enzyme A or co-acetylase.[1]

Combined with β mercaptoethylamine it forms a substance called pantetheine or the *L bulgaricus* factor [6] This substance, after phosphorylation is a precursor of co-enzyme A which is formed by further addition of diphosphoadenosine The co enzyme A molecule has a molecular weight of about 767 and may exist in the reduced (—SH) or in the oxidized (S—S) forms In the oxidized state the disulfides may be mixed, that is β mercaptoethylamine may form one part and cysteine, glutathione or one of several thiols may form the other [4,5] The structure of this large molecule is still tentative and probably will require revision in the light of future degradation experiments when it has been obtained in complete purity

Co-enzyme A, together with a specific protein apoenzyme, functions in many reversible acetylation reactions Acetyl co-enzyme A, the activated molecule, may be regarded as a pivot on which acetyl transfer mechanisms turn This implies that it may, under suitable conditions, act as either an acetyl acceptor or acetyl donor The —SH— end of the molecule is the active portion It will accept an acetyl group from acetyl phosphate when another enzyme, phosphotransacetylase is present, or from acetate, when adenosine triphosphate is present The acetate radical may be transferred to oxaloacetate to form citrate (a process which is necessary for the initiation of the energy liberating Krebs cycle) to choline to form acetyl choline, to another acetate molecule to form aceto acetate or to glycine to form acetyl glycine It is active in the acetylation of sulfa drugs, of para amino benzoic acid and glucosamine It accepts acetyl radicals formed in the oxidation of pyruvate citrate and fatty acids and transfers them elsewhere It conjugates not only with acetyl, but also acyl groups, for instance benzoyl COA + glycine → hippuric acid It is also active in porphyrin formation and in the synthesis of cholesterol steroids, and fatty acids [7–9] It bears the same relation to the two carbon unit that folic acid and vitamin B_{12} bear to the single carbon unit, and like these vitamins is of extraordinary importance in cellular metabolism



Pantothenic Acid Deficiency States in Animals.—Pantothenic acid deficient animals exhibit a wide variety of syndromes with certain common denominators.[8] Pantothenic acid deficient chicks develop dermatitis, spinal cord degeneration, involution of the thymus and fatty degeneration of the liver. In addition, ducks, deficient in pantothenic acid, develop anemia due to the interruption of the normal synthetic pathways for heme.[8a] Black rats develop gray hair, anemia, leukopenia, adrenal hemorrhage and necrosis, gonadal atrophy, infertility, duodenal ulcer and produce antibody only at a very slow rate.[10] Dogs develop hypoglycemia, fatty liver, gastrointestinal tract disturbances, and convulsions. Pigs lose their hair, have excessive nasal secretions, diarrhea, ulcerative colitis and degenerative lesions of the spinal cord and peripheral nerves.[13]

The adrenal necrosis which occurs in pantothenic acid-deficient rats may be the result of (1) failure of 11-oxysteroid production because pantothenic acid is involved in this synthesis or (2) excessive "stress" which places so great a demand upon the adrenocortical mechanism that adrenal exhaustion results. It is likely that both (1) and (2) are involved and lead to a vicious cycle resulting in adrenal necrosis. Experimental support for (1) has been obtained.[13a]

Several interesting biological relationships have been observed. Adrenalectomized rats on a pantothenic acid-deficient diet do not develop gray hair, but such rats treated with desoxycorticosterone or cortical extracts do.[14,15] Pantothenic acid protects rats from the deleterious effects of severe stress and together with salt, will maintain adrenalectomized rats in reasonably good health. It is obvious from these observations that there is a very close relationship between pantothenic acid and the functions of the adrenal cortex.

Human Physiology.—The amount of pantothenic acid consumed daily with 2500 calories of an adequate diet is approximately 10 mg.[5] Normal adult human beings excrete 1 to 7 mg. of pantothenic acid in the urine daily.[11] The blood levels range between 19 and 32 μ/100 cc. in one series[17] and 3 to 10 μ/100 cc. in another.[7] Patients with chronic malnutrition tend to have lower levels in blood and urine but there is so much overlapping in these levels and in those obtained after administering a test load of 10 to 50 mg. of the vitamin that such procedures are not very helpful in the diagnosis of pantothenic acid deficiency.[16,6] Recently, the degree of acetylation of a test dose of sulfanilamide or para amino benzoic acid has been used to demonstrate physiologic impairment of acetylation reactions and may be applied to the detection of pantothenic acid deficiency states.[18,19]

Co-enzyme A does not circulate in the blood and appears to pass cell membranes with difficulty. Presumably it is synthesized intracellularly wherever needed from pantothenic acid and other components. Such synthesis has been demonstrated in cell-free liver filtrates. Organs with the highest co-enzyme A content are listed in order of decreasing concentration: liver, adrenal, kidney, brain, heart, testis.

Gordon[1] has reported that pantothenic acid has afforded relief in nutritional neuropathy and Korsakoff's psychosis and Goplan,[20] Glusman,[21] and Denny-Brown have observed improvement in the burning or

electric foot syndrome which was noted in prisoners of the Japanese during World War II Sarma has reported modest reductions in acetylated para amino benzoic acid in persons with this syndrome [19]

The early reports that pantothenic acid was an anti gray hair factor in human beings have not been corroborated [1] nor have reports been confirmed that pantothenic acid will relieve postoperative paralytic ileus [3]

Ralli has reported very interesting results suggesting that pantothenic acid will improve the ability of well nourished subjects to withstand stress and has bolstered her findings with biochemical corroborative evidence [24]

Bean and his co-workers have induced pantothenic acid deficiency in human volunteers by a pantothenic acid deficient diet and a pantothenic acid antagonist, omega methyl pantothenic acid [3, 8] Fatigue malaise headache, sleep disturbances nausea abdominal cramps epigastric distress, occasional vomiting and an increase in flatus occurred Their subjects developed parasthesias in the extremities muscle cramps and impaired coordination The eosinopenic response to ACTH was lost and increased sensitivity to insulin developed but there was no change in the urinary 17-ketosteroid or in blood or urine sodium levels Low blood cholesterol and potassium levels and decreased acetylation of para amino-benzoic acid reported in previous communications were caused by the experimental plan and individual variation rather than by pantothenic acid deficiency [8] These investigators were unable to prove that pantothenic acid deficiency induced by their methods interfered with adreno-cortical function Most of the symptoms and laboratory abnormalities ascribed to the pantothenic acid deficiency were reversed by the administration of large doses of pantothenic acid

It is evident that pantothenic acid plays a most important role in human nutrition but it is doubtful that pantothenic acid deficiency occurs except under most unusual circumstances or as a result of excessive metabolic demands

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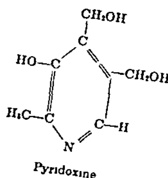
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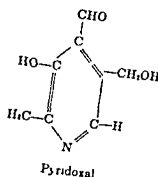
THE VITAMIN B_6 GROUP

By RICHARD W VILTER

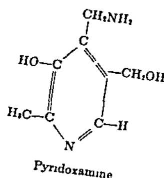
Pyridoxine pyridoxal, pyridoxamine and pyridoxal phosphate, collectively, are called the vitamin B_6 group The term, pyridoxine, or the other specific chemical names are used only when reference is made to one of these chemical compounds



Pyridoxine



Pyridoxal



Pyridoxamine

Distribution of Vitamin B_6—Vitamin B_6 occurs in animal products largely in its pyridoxal and pyridoxamine forms Pyridoxine is the largest component in products of vegetable origin [1] Each of the three forms is equally active in animals when given by injection, but pyridoxine is the most active when given without food via the gastrointestinal tract, presumably because it is absorbed by intestinal organisms less than the others [1a]

The average adequate human diet contains between one and two milligrams of vitamin B_6 A wide variety of foods contain this vitamin as indicated in Table 28 Studies on intake and output of vitamin B_6 in human beings indicate that the amount of pyridoxine lost in the stool is reasonably constant over a wide range of intake In adult persons it ranges from 0 7 to 0 9 mg per day and in infants from 0 15 to 0 30 mg per day

TABLE 28 — VITAMIN B_6 CONTENT OF SELECTED FOODS
(μg Per 100 Grams or 100 cc Edible Portion)

Cow's milk	65–73	Frozen fish	110
Human milk	3 5–22	Whole wheat	270–410
Evaporated milk	25–41	Wheat germ	1030–1120
Condensed milk	33–49	Rolled oats	190–250
Whole milk		Rye	370
Spray dried	46–48	Yellow corn	250–570
Skimmed milk		Corn grits	250
Spray dried	50–56	Raw milled rice	150
Lamb		Soybean flour	710–800
Leg	290–460	Split peas	190–400
Roast leg	120	Frankfurter	130
Pork		Eggs	22
Ham	330 580	Oranges	80
Cured ham	190	Apples	26
Loin	270	Bananas	300
Beef		Cabbage	290
Liver	710–810	Cauliflower	20
Round	370	Lettuce	71
Kidney	390–1020	Peas (fresh)	50–190
Heart	290	Peanuts	300
Brain	160	Potatoes (Irish)	160
Veal		Spinach	83
Leg	370	Turnips	100
Roast leg	200		
Shoulder	300		
Roast shoulder	140		

These values have been compiled from data given by Sarma P S Snell E F and Elvehjem C A Jr Nutrition *33* 121 1947 Macy I G Am Jr Dis Children *78* 589 1949 Hassinen J B Durbin G T and Bernhart F W Jr Nutrition *53* 249 1954 Rabinowitz J C and Snell E F Jr Biol Chem *176* 1157 1948 Cheldelin & Williams University of Texas Publication No 4237 p 105

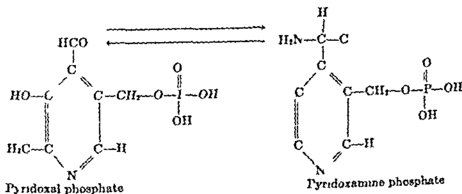
Pyridoxic acid is the largest excretory product of the vitamin B_6 group found in the urine When the method of Huff and Perlzweig[15] is used to measure 4 pyridoxic acid it appears that persons on a normal diet without vitamin B_6 supplementation excrete more vitamin B_6 metabolites than they get from their diets *For instance* Linkswiler *found that persons* on an average intake of 0 76 mg of vitamin B_6 excreted in the urine 2 38 mg of 4-pyridoxic acid and 0 09 mg of other vitamin B_6 compounds Such data suggested that human beings absorbed considerable vitamin B_6 synthesized by intestinal organisms For some time investigators have known the Huff and Perlzweig method for 4-pyridoxic acid gave falsely high values because of fluorescent substances in the urine which interfered

with the test when 4-pyridoxic acid levels were low The degree of interference was not appreciated until Reddy, Reynold and Price[3] published a chromatographic method which eliminated the interfering substances Actual values for 4-pyridoxic acid are about ¼ to ⅓ of those obtained by the old assay method Thus, intakes balance quite well with urinary outputs and, since vitamin B_6 in food is absorbed almost completely from the upper gastroenteric tract, there appears to be little absorption of the vitamin produced by the enteric microorganisms in the colon Studies[4,5] in which enteric microorganisms have been greatly reduced in numbers by the administration of unabsorbable antibiotics have not demonstrated any appreciable contribution of these microorganisms to the vitamin B_6 supply of human beings, though apparently the rat does derive some of the vitamin from such sources[6]

Persons on an adequate diet have, on the average 5μg/100 cc of vitamin B_6 in the blood as determined by *S Carlsbergensis* assay[7] Most of the B_6 is in the blood cells Pyridoxal phosphate levels in human blood determined by the method of Umbreit, Bellamy and Gunsalus[8] are on the average below 10 millimicrograms per ml[9] Pyridoxal phosphate levels of children under 18 months of age are higher, averaging 32 mμg/ml These values are quite low if compared with those of laboratory animals which range from 32 to 187 mμg/ml The pyridoxal phosphate levels in leukocytes of adults are 0 14–0 15 mμg/10^6 leukocytes, and of children are 0 24–0 38 mμg/10^6 leukocytes Administration of pyridoxine increases the pyridoxal phosphate level of whole blood within 3 days and of leukocytes within 10 days A total of 7 mg of pyridoxine per day appears to be all that the human body can convert into the coenzyme form Ingestion of larger amounts does not cause further elevation of the pyridoxal phosphate levels[9a]

Several common nutrients increase the need for vitamin B_6 in animals Among these are methionine,[10] protein,[11] linseed oil[12] and sucrose[13] On the other hand certain substances such as choline, aureomycin, essential fatty acids, biotin, dextran and pantothenic acid seem to decrease the requirements[14] Many of these relationships may be due to effects on bacterial synthesis of B_6 Others are probably due to sparing effects on B_6 metabolism within the body

Biochemical Functions of Vitamin B_6—Pyridoxal phosphate functions biochemically as a co enzyme for transaminase,[15] codecarboxylase,[16] deaminase, desulfurase and many other enzyme systems[17] Transamination, the transfer of amino groups, is probably mediated through the inter



Pyridoxal phosphate

Pyridoxamine phosphate

conversion of pyridoxal phosphate and pyridoxamine phosphate The co enzyme is necessary also for the conversion of tryptophan to the pyridine co enzymes (cozymase, a co-enzyme containing nicotinic acid) [19,21] Side products of this reaction are xanthurenic acid 3 hydroxykynurenine kynurenine and kynurenic acid, which appear in the urine in abnormally large amounts when the normal metabolic pathway of tryptophan to n^1-methyl nicotinamide is blocked by a deficiency of vitamin B_6 [1a] This vitamin is necessary also for the formation of serotonin (5-hydroxytryptamine) from tryptophane [1b] and of γ aminobutyric acid from glutamic acid [1c] It is involved in essential fatty acid metabolism [6] and activates glycine, making possible the transfer of a single carbon unit from this amino acid to tetrahydrofolic acid [21d]

Several biochemical tests for vitamin B_6 deficiency have been proposed When alanine is given to vitamin B_6 deficient animals urea nitrogen remains elevated for more than twelve hours, suggesting impairment of deamination[13] or as has been suggested, increased protein catabolism for energy purposes [3] A second and simpler test is based on the fact that xanthurenic acid, an abnormal product of tryptophan metabolism, appears in the urine of vitamin B_6 deficient animals [0] and human beings [6 38] after feeding of tryptophan

Vitamin B_6 Deficiency States in Animals —Vitamin B_6 deficiency induces in rats a syndrome characterized by dermatitis which resembles human seborrheic dermatitis muscular weakness convulsive seizures decrease in lymphoid tissue lymphopenia polymorphonuclear leukocytosis decrease in circulating antibodies [18] increased receptivity for homografts [18] increased output of xanthurenic acid and decreased output of n^1-methylnicotinamide in the urine after a test dose of tryptophan [20 21] increased blood urea nitrogen levels and sustained urea production for longer than twelve hours after a test dose of alanine [2] Growth slows down fat is depleted but nitrogen balance remains positive and there is no demonstrable deficiency of protein in the tissues [3] These data are interpreted to indicate that pyridoxine deficiency interferes with the ready availability of energy from carbohydrate and fat sources and that under these circumstances energy is derived *from protein* A *similar situation concerning fat* and protein has been found in rats with other vitamin B complex deficiency states It is not peculiar to pyridoxine deficiency

The dermatitis of pyridoxine deficient rats is similar though probably not identical to the dermatitis which develops as the result of essential fatty acid deficiency A high fat diet will delay the appearance of pyridoxine deficiency dermatitis [4] and pyridoxine has a similar effect on the dermatitis of essential fatty acid deficiency [5] Vitamin B_6 also is necessary for the interconversion of fatty acids, particularly for the conversion of linoleic acid to arachidonic acid in these animals [6]

Dogs develop hypochromic anemia high serum iron levels [7] and atherosclerosis [7a] Swine develop a similar anemia, low levels of free erythrocyte protoporphyrin and signs of central nervous system disorder [5] Monkeys exhibit the seborrhea like dermatitis, weakness lymphocytopenia, polymorphonuclear leukocytosis atherosclerosis[31] and, like other animals, excrete xanthurenic acid in the urine after the ingestion of tryptophan [22]

These data link vitamin B_6 to the metabolism of protein and amino acids, carbohydrate, fat, and other energy sources, porphyrin, iron and essential fatty acids. There is evidence also linking vitamin B_6 to nucleic acid metabolism,[30d] and to adrenocortical activity.[9] Both biochemically and physiologically it seems to be a substance of very great metabolic importance.

Vitamin B_6 Deficiency in Human Beings.—In 1939, Spies, Bean and Ashe[33] described an ill-defined syndrome characterized by weakness, nervousness and irritability, insomnia and difficulty in walking in patients on poor diets. These symptoms did not respond to treatment with other members of the vitamin B-complex but were relieved within twenty four hours when pyridoxine was administered. In the same year, Smith and Martin[34] reported that pyridoxine was effective in healing cheilosis which did not respond to riboflavin. Much more recently Hawkins and Barsky[35] administered a purified diet deficient in vitamin B_6 to a normal adult person for fifty-four days. No clear-cut symptoms of pyridoxine deficiency appeared though mental depression was noted by the investigators. Greenberg and Rinehart[36] observed that the excretion of xanthurenic acid after the ingestion of tryptophan was greatly increased in two adult persons who had subsisted for three weeks on a diet low in vitamin B_6. This defect was rectified by pyridoxine. Convincing evidence of a pyridoxine deficiency state induced in human infants by synthetic diet alone has been presented by Snyderman, Carretero and Holt.[37] Pyridoxic acid disappeared from the urine of these infants at an early date. They ceased to gain weight after several months. Convulsions occurred in one and hypochromic anemia in the other. N′-methylnicotinamide excretion in the urine after a test dose of tryptophan was decreased below control values. All of these abnormalities were relieved by the administration of pyridoxine. The slowest to disappear was the abnormality in N′-methylnicotinamide output.

Pyridoxine deficiency has been induced in 50 adult human beings by Vilter and his associates.[38] 4-desoxypyridoxine, a pyridoxine antagonist was used. Symptoms and signs appeared more rapidly and at a lower dose of desoxypyridoxine when the diet was deficient in the entire B-complex. Patients on adequate hospital diets also developed the lesions after a longer period on a higher dose of desoxypyridoxine. Seborrhea-like lesions appeared about the eyes, in the naso-labial folds and around the mouth. These lesions spread to involve the face, forehead, eyebrows and the skin behind the ears. The scrotal and perineal regions were involved occasionally. Intertrigo developed under the breasts and in other moist areas. Hyperpigmented scaly pellagra-like dermatitis also developed occasionally in the collar region and on the forearms, elbows and thighs. Cheilosis, glossitis and stomatitis occurred which were morphologically indistinguishable from the oral lesions of niacin and riboflavin deficiency. Three patients developed peripheral neuropathy of a sensory type, motor function was impaired later. These investigators noted weight loss in all patients, apathy, somnolence and increased irritability in some. There was a strong tendency to develop infections particularly of the genito urinary tract. The majority of the patients, including all those who developed clinical signs of deficiency, excreted large amounts of xanthurenic acid in the urine after a test dose of tryptophan but their ability to convert tryptophan to

N^1-methylnicotinamide was not impaired, perhaps because this reaction takes place to a minor extent in the adult person Lymphopenia was noted but though anemia occurred in some of these patients it could not be related definitely to the B_6 deficiency state

Supplements of thiamin, riboflavin and nicotinamide had no effect on the skin, mucous membranes or peripheral nerve lesions Linoleic acid in large doses relieved the skin lesions but allowed the other manifestations to progress Prompt regression in all lesions followed the administration of pyridoxine, pyridoxal or pyridoxamine in doses as low as 5 mg daily

Vitamin B_6 deficiency has been implicated also in the genesis of a convulsive disorder which has occurred in infants fed from birth on certain commercial liquid milk formulae Pyridoxine has in several instances relieved these convulsions and the abnormal electroencephalographic tracings associated with them [39]

For at least ten years pyridoxine has been used by obstetricians for the control of nausea and vomiting of pregnancy This usage was quite empirical and the effectiveness of this treatment has not been proved by carefully controlled studies However there is evidence that pyridoxine metabolism may be altered during human pregnancy McGanity and his associates[40] have demonstrated that pregnant women have lower blood urea nitrogen levels on the average than non pregnant women and the lowest levels occur in women with hyperemesis gravidarum They showed also that after a test dose of alanine the blood urea nitrogen remains elevated for more than twelve hours in women with hyperemesis gravidarum whereas it has returned to normal levels by this time in non pregnant women and women with uncomplicated pregnancy Administration of pyridoxine restored the relationships found in the latter group Wachstein and Gudaitis[41] have shown that pregnant women in the second and third trimester given a test dose of tryptophan excrete abnormally large amounts of xanthurenic acid in the urine when compared with non-pregnant women and that this abnormality is quickly relieved by pyridoxine They have reported that pregnant women excrete a smaller amount of 4-pyridoxic acid in the urine than do non-pregnant women after a test dose of pyridoxal [4] and that the buffy coat pyridoxal phosphate levels of pregnant women are lower than levels found in a non pregnant control group [4] The differences however, are not large and Wachstein's values for pregnant women are approximately the same as Boxer reported for a non pregnant group of women [9] Friedman and his associates confirmed the abnormality in tryptophan metabolism during and immediately after pregnancy but found that urine and skin vitamin B_6 levels were similar in pregnant and non pregnant women [4,5] These investigators proposed that pregnancy in some way increases the need for vitamin B_6 particularly in regard to tryptophan metabolism rather than that the fetus depletes the pregnant woman of vitamin B_6 because of its large vitamin B_6 requirement

Isonicotinic acid hydrazide an anti tuberculosis drug [4] hydralazine an anti hypertensive drug [4] and other related compounds produce convulsions in animals and peripheral neuritis in human beings These lesions occur because these drugs interfere with certain activities of pyridoxal

phosphate It is likely that pyridoxal combines with the hydrazides to form pyridoxal hydrazones which are metabolically inactive A large amount of vitamin B_6 is excreted in the urine combined with hydrazide, and xanthurenic acid 3-hydroxykynurenine and kynurenine appear in the urine after a tryptophan load is given Pyridoxine will prevent or reverse the neuritis and stop the convulsions

Several infants with convulsive seizures dating from shortly after birth have been found to respond to 2 mg of pyridoxine daily [illegible] Some have shown abnormalities of tryptophan metabolism, others have not Those who have this metabolic defect require much more pyridoxine to correct it than do otherwise normal infants placed on a vitamin B_6 deficient diet The convulsions recur when pyridoxine treatment is stopped For these reasons it is probable that there is a metabolic defect in these infants which greatly increases vitamin B_6 requirement for normal cerebral metabolism Perhaps it is lack of γ amino butyric acid that allows the convulsions to occur In adults 'rum fits' have been linked with vitamin B_6 deficiency [illegible]

Several patients with hypochromic anemia, whose serum and bone marrow iron levels are high, have responded to pyridoxine in daily doses of 10 mg or more [illegible] These patients had failed to respond to all other hematopoietic vitamins and minerals They, too are thought to have a metabolic block probably involving porphyrin formation, which greatly increases the requirement for vitamin B_6

Jolliffe[43] has reported that patients with Parkinsonism have been benefited by pyridoxine Other investigators have failed to confirm this A similar situation pertains to the effect of this vitamin in pseudohypertrophic muscular dystrophy,[44] drug induced neutropenia,[45] and acne vulgaris[46]

A rough estimate of human vitamin B_6 requirements can be made from certain animal experiments Elvehjem and his associates[47] showed that there was insufficient vitamin B_6 activity in the army K rations to support normal growth of rats When the content was doubled to provide a concentration of 200 micrograms of vitamin B_6 per 100 gm of ration, growth of the rats proceeded at a normal rate It was estimated by extrapolation that this would indicate a requirement of 1 5 mg of vitamin B_6 per day for human beings Similar rough calculations from data obtained in deoxypyridoxine experiments indicate that about 1 to 2 mg are required per day This is the amount which the average adequate diet will contain The widespread availability of pyridoxine in natural foods, probably explains why pyridoxine deficiency is so seldom recognized under natural conditions in human beings

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phosphate It is likely that pyridoxal combines with the hydrazides to form pyridoxal hydrazones which are metabolically inactive A large amount of vitamin B_6 is excreted in the urine combined with hydrazide and xanthurenic acid 3-hydroxykynurenine and kynurenine appear in the urine after a tryptophan load is given Pyridoxine will prevent or reverse the neuritis and stop the convulsions

Several infants with convulsive seizures dating from shortly after birth have been found to respond to 2 mg of pyridoxine daily[39,40] Some have shown abnormalities of tryptophan metabolism, others have not Those who have this metabolic defect require much more pyridoxine to correct it than do otherwise normal infants placed on a vitamin B_6 deficient diet The convulsions recur when pyridoxine treatment is stopped For these reasons it is probable that there is a metabolic defect in these infants which greatly increases vitamin B_6 requirement for normal cerebral metabolism Perhaps it is lack of γ amino butyric acid that allows the convulsions to occur In adults 'rum fits' have been linked with vitamin B_6 deficiency[41]

Several patients with hypochromic anemia, whose serum and bone marrow iron levels are high have responded to pyridoxine in daily doses of 10 mg or more[42] These patients had failed to respond to all other hematopoietic vitamins and minerals They, too are thought to have a metabolic block probably involving porphyrin formation which greatly increases the requirement for vitamin B_6

Jolliffe[43] has reported that patients with Parkinsonism have been benefited by pyridoxine Other investigators have failed to confirm this A similar situation pertains to the effect of this vitamin in pseudohypertrophic muscular dystrophy,[44] drug induced neutropenia,[45] and acne vulgaris[46]

A rough estimate of human vitamin B_6 requirements can be made from certain animal experiments Elvehjem and his associates[47] showed that there was insufficient vitamin B_6 activity in the army K rations to support normal growth of rats When the content was doubled to provide a concentration of 200 micrograms of vitamin B_6 per 100 gm of ration, growth of the rats proceeded at a normal rate It was estimated by extrapolation that this would indicate a requirement of 1 5 mg of vitamin B_6 per day for human beings Similar rough calculations from data obtained in deoxypyridoxine experiments indicate that about 1 to 2 mg are required per day This is the amount which the average adequate diet will contain The widespread availability of pyridoxine in natural foods, probably explains why pyridoxine deficiency is so seldom recognized under natural conditions in human beings

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FOLIC ACID

By Richard W Vilter

Introduction —Folic acid has been called folacin (American Institute of Nutrition) pteroylglutamic acid (P G A), the lactobacillus casei factor, vitamin Bc vitamin M, vitamin U and many other names Usage has shown preference for folic acid or folacin

In 1945 folic acid was obtained from liver and was synthesized by Angier and his associates [1] This report brought to successful conclusion years of searching for a factor necessary for the growth of many species of animals and microorganisms, and for the protection of man monkeys, rats, chicks and ducks against leukopenia and anemia In 1921, McCarrison[2] noted that monkeys maintained on a diet deficient in "vitamin B" developed diarrhea and anemia In 1934, Lucy Wills[3,4] recognized that there was a factor in yeast and crude liver extracts but not in the refined types which would relieve tropical macrocytic anemia She reproduced a similar clinical picture in monkeys on a polished rice, margarine, fruit diet and showed that the same crude extracts of liver and yeast would eliminate the pathology [5,6] This factor was called the "Wills factor" Day, Langston and Shukers in 1935 induced a syndrome of anemia, leukopenia diarrhea and stomatitis in monkeys Later they called this vitamin M deficiency and recognized that it was similar to sprue [7] In 1938, Stokstad and Manning[8] described a growth factor for chicks which they named vitamin U and in 1939, Hogan and Parrott[9] reported observations on a factor which they called vitamin Bc, an antianemic substance for chicks Snell and Peterson[10] described a new growth factor for lactobacilli in 1940 the lactobacillus casei factor and Mitchell Snell and Williams[11] obtained the substance in concentrated form from deep green leaves This source suggested the name folic acid Late in 1945 Day and his associates[12] successfully treated vitamin M deficiency in monkeys with folic acid and Pfiffner[13] related folic acid to the chick factor vitamin Bc Soon it became apparent that all these factors were one and the same substance or conjugates of it though the exact relationship of the Wills factor to folic acid is not yet completely clear

In rapid succession, thereafter, reports appeared concerning its beneficial hematopoietic effect in pernicious anemia [14,15] nutritional macrocytic anemia [14,16] sprue [17] pernicious anemia of pregnancy,[15,18] liver extract refractory megaloblastic anemia (achrestic anemia)[19,20] megaloblastic anemia of infancy [1,22] and other less common types [23,24] Sauberlich and Bauman[25] reported on a new growth factor for L citrovorum called the citrovorum factor* (folinic acid) which later was shown to be a formyl derivative of reduced folic acid, and a successful competitor with aminopterin [26] Natural citrovorum factor from liver has been prepared by Keresztesy and Silverman [7] and is twice as active as the synthetic material A number of folic acid coenzyme forms have been recognized and will be discussed in a later section of this chapter

*Though the organism which was thought to be L citrovorum has been shown to be Pediococcus cerevisiæ, the term Citrovorum factor (CF) has been retained

Natural Sources and Physiology —Folic acid is a yellow crystalline compound that occurs widely distributed in nature. Deep-green leafy vegetables and liver are very rich in it and Table 29 gives some comparative values for other foods. It is actually a member of a family of closely related substances. Both folic and folinic acids occur in foods as conjugates of glutamic acid. The heptaglutamates of folic acid (vitamin Bc conjugate) and folinic acid containing seven glutamic acid residues and the triglutamates of folic acid (the fermentation factor teropterin) are the only ones which occur in nature. The diglutamate of folic acid (diopterin) has been synthesized. These conjugates are broken down in the body by enzyme systems found in the tissue. These enzymes are called conjugases. Conjugase inhibitors are present in some crude preparations of folic acid conjugate. These inhibitors found particularly in yeast extracts inhibit the action of the tissue conjugases and prevent the liberation of free folic acid. Apparently the same conjugases split the folic or folinic acid conjugates,[28] liberating free folic or folinic acids the formulæ of which are given below.

Tetrahydrofolic acid a reduction product of folic acid plays a central role in the various chemical reactions which folic acid catalyzes. The actual reduction process is favored by the presence of triphosphopyridine nucleotide and ascorbic acid or other reducing agents.[28a, 9] Folic acid antagonists, aminopterin and amethopterin inhibit this reaction in a noncompetitive fashion.[9a] From tetrahydrofolic acid which is an extremely unstable and reactive compound a number of related substances can be formed. A formyl group (—CHO) an hydroxymethyl group (—CH OH) or a formimino group (—CH=NH) can be attached to position N^5 or N^{10}. After removal of water or ammonia cyclic compounds can be formed in which the one carbon unit is attached to both N^5 and N^{10} positions. Any or all of these may be called folic acid coenzymes.[9b] (See Fig 25)

An average human diet selected from a wide variety of foods supplies 0.5 to 1.0 mg of folic acid compounds daily most of it in conjugated form. Folinic acid taken orally is converted largely to folic acid in the gastrointestinal tract. Folic acid is readily absorbed from both upper and lower portions of the tract but there is no information on how much of the folic or folinic acids produced by the intestinal microorganisms is available to the human host. It is probable that at least some is obtained from this source. Aureomycin[34] and ascorbic acid[35] may favor production or availability of this folinic acid.

The level of folic acid in the serum is about 1.5 mμg/ml [36, 37] and may rise as high as 12 mμg/ml one to four hours after an oral dose of 1 mg of folic acid. Much higher levels are obtained after larger doses of folic acid are administered. 15 mg may elevate the serum level to 400 to 600 mμg/ml. The folinic acid level of the serum is about 0.8 mμg/ml and does not rise appreciably after a test dose of folic acid given by mouth or intravenously but folic acid is converted in the body to folinic acid.[35] One-tenth to 1.0 per cent of the test dose of folic acid will appear in the urine as folinic acid[34, 37] and 10 to 30 per cent as folic acid.[30, 33] The rest cannot be traced. In patients with scurvy who are given test doses of folic acid there is little increase in folinic acid in the urine until five or six days after ascorbic acid

TABLE 29 —FOLIC ACID CONTENT OF FOODS*
(Fresh Weight Basis—mg /100 gm)

Food	*Washington, D C Market*	*Texas Market*
Meats		
Beef		
Round steak	0055- 0066	0142- 0167
Kidney		0584
Liver		2941
Lamb		
Stew meat ground	0025	
Leg		0033
Pork		
Loin	0032	
Vegetables fresh		
Asparagus	0893	1425
Beans, lima	0466	0103- 0562
Beans green snap	0172- 0228	0136- 0406
Beets	0150	0106
Broccoli	0352	0236- 0245
Cabbage	0064- 0114	0171- 0426
Carrots	0054- 0076	0062- 0156
Corn, sweet	0093	0083- 0699
Cauliflower	0172	0291- 0299
Greens spinach	0486- 1053	0522- 1145
Peas	0015- 0355	0203- 0269
Potatoes whole	0135	0061
Poultry		
Chicken		
Dark		0028
White		0031
Eggs, whole	0032	0075
Fruits fresh		
Apples	0005- 0006	
Bananas	0109	0082
Strawberries	0046	0061
Cherries bing	0067	0052
Grapefruit	0022	0033
Lemons	0078	
Oranges	0055	0047
Bread		
Cracked wheat	0250	
White	0138	
Breakfast cereals		
Cornflakes	0050	
Wheat bran	0796	
Wheat, shredded	0292- 0716	
Dairy products		
Buttermilk		0111
Pasteurized		0006

* United States Department of Agriculture, *Bureau of Human Nutrition and Home Economics, Agriculture* Handbook No 29 1952

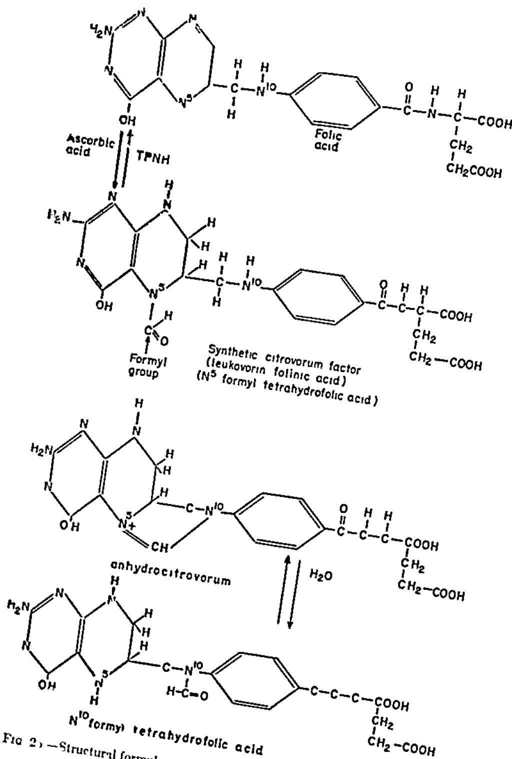


FIG 2 —Structural formulæ of folic acid folinic acid and some of the tetrahydrofolic acid coenzymes

is given[33] indicating the need for ascorbic acid or other reducing agents for this conversion. About 50 per cent of patients with pernicious anemia in relapse have subnormal folic acid levels in the blood[33a] and excrete somewhat less of a test dose of folic acid in the urine than normal persons or persons with other types of anemia.[34-37] After a test dose, however, patients with pernicious anemia will have the same rise in serum levels which occurs in normal persons. Persons with sprue absorb folic acid poorly.[37a]

Biochemistry of the Folic Acid Group.—The folic acid coenzymes are extremely important biological catalysts as indicated by studies with microorganisms, liver slices and laboratory animals. They function in the transfer of single carbon units, a subject thoroughly reviewed by Welch and Nichol.[40] It is likely that the formyl, hydroxymethyl, methylene or *formimino groups transferred to tetrahydrofolic acid may be, in turn,* donated to other compounds, thus accomplishing single carbon unit transfers. In this way the following interconversions may occur: Serine⇄glycine, imidazole carboxamide⇄inosinic acid, homocysteine⇄methionine (this reaction not shown to be reversible) and creatine⇄guanido acetic acid. In addition, these coenzymes take part in thymidine synthesis, the cleavage of formimino glycine and formimino glutamic acid (the latter derived from histidine*), the formylation of glutamate, the synthesis of choline, the exchange of formate into pyruvate and the hydroxylation of phenylalanine to form tyrosine. In massive doses, folic acid will decrease the output of parahydroxyphenyl pyruvic and lactic acids in the urine of scorbutic infants given a test dose of tyrosine.[46] It is involved, also, in the formation of the porphyrin ring and therefore in hemoglobin metabolism.

Allusion has already been made to its important functions in the formation *and metabolism of purines and pyrimidines. Bacterial growth studies* support these biochemical observations. Thymine or thymidine will replace folic acid as growth factor for *L. casei* or *Strep. faecalis* when purines are available. In the absence of folic acid or when an antagonist, methyl folic acid is used, *L. casei* will not form normal amounts of desoxyribose nucleic acid. This defect can be overcome by the addition of large amounts of thymine. Under these conditions, ribose nucleic acid production is increased also.[4, 43] Megaloblastic anemia in human beings may respond to thymine, uracil, orotic acid, and sometimes to histidine, methionine[43a, 54] and choline. These observations emphasize some of the metabolites in the synthesis of which folic acid is involved.

Other Physiologic Effects of the Folic Acid Group.—In animal nutrition folic acid is important for the activity of certain hormones. For instance, estrogens *have no effect on the oviducts of young folic* acid-deficient chicks until folic acid is given.[44] It is important also for the maintenance of normal pregnancy in rats and for the prevention of congenital anomalies.[45]

Aminopterin (4-aminopteroyl glutamic acid) and amethopterin (4-amino-N[10]-methylpteroyl glutamic acid) are potent metabolic antagonists of the

*A test for folic acid deficiency has been *proposed* based on the excretion of excessive amounts of formimino glutamic acid in the urine under these conditions. After heat hydrolysis, this material is found as extra glutamic acid.[43b]

folic acid family These substances interfere with the conversion of folic acid and with the metabolic effects of folinic acid These antagonisms are readily reversed by folinic acid but not by folic acid Three mg of folinic acid parenterally will reverse the effects of 1 mg of aminopterin more effectively than will 200 to 400 mg of folic acid [6]

There is some evidence that vitamin B_{12} deficiency may induce a secondary deficiency in the folic acid co-enzyme either by reducing the amount of folic or folinic conjugates converted to folic or folinic acids[33,46] or the amount of folic acid coenzymes formed[47] In the absence of vitamin B_{12} redox potentials may not be suitable for the conversion of folic acid to tetrahydrofolic acid Ascorbic acid deficiency may interfere with folic acid metabolism in a similar manner [9] Perhaps such metabolic abnormalities as these may explain how a person with pernicious anemia (a conditioned vitamin B_{12} deficiency) becomes sufficiently deficient in folic acid to respond temporarily to this substance and why the tissues of such a person have a greater avidity for folic acid than is normal Such abnormalities may also explain why ascorbic acid treatment occasionally induces reticulocytosis in persons with pernicious anemia in relapse and why persons with severe scurvy sometimes have megaloblastic anemia responsive to ascorbic acid

Folic or folinic acid deficiency states have not been induced in healthy human beings However, a deficiency state has been induced in monkeys[7] and swine[48,49] on a folic acid-deficient diet bolstered by a sulfa drug and a folic acid antagonist In monkeys particularly, the resulting syndrome is very much like human sprue Diarrhea glossitis, megaloblastic anemia and abnormalities in gastro intestinal tract absorption develop The syndrome is relieved rapidly by folic acid but only partially and temporarily by refined liver extract or vitamin B_{12} Monkeys on a milk diet deficient in ascorbic acid and folic acid develop scurvy and megaloblastic anemia after about ninety days [50,51] Folic acid rapidly eliminates the megaloblastosis ascorbic acid relieves the scurvy and somewhat more slowly the megaloblastic anemia Vitamin B_{12} has no beneficial effect This type of megaloblastic anemia in monkeys may develop because ascorbic acid deficiency interferes with folic acid metabolism either at the points of conversion of folic acid conjugate to folic acid or of folic acid to folic acid coenzymes No supporting evidence of a chemical type for this theory has been obtained in the monkeys and it may be that the scorbutic state merely acts as a stress which increases greatly the requirement for folic acid [51]

Therapeutic Effects of the Folic Acid Group in Man —In man folic acid is a potent panhematopoietic agent It relieves the anemia and glossitis of pernicious anemia temporarily, but allows the neurologic degeneration to continue [5] It relieves the anemia, glossitis and gastro-intestinal dysfunction of the sprue syndrome, nutritional macrocytic anemia and tropical macrocytic anemia and is eminently effective in pernicious anemia of pregnancy, megaloblastic anemia of infancy and vitamin B_{12} refractory megaloblastic anemia (achrestic anemia) It will relieve the pernicious anemia like syndrome following total gastrectomy and infestation with the fish tape worm (Diphyllobothrium latum) In the latter two syndromes, which are the result of conditioned lack of vitamin B_{12} the same contraindications to its use hold as in the case of pernicious anemia

TABLE 30.—THE CLINICAL VARIETIES OF MEGALOBLASTIC ANEMIA TOGETHER WITH SOME IMPORTANT CLINICAL MANIFESTATIONS, THE PROBABLE DEFICIENCY INVOLVED IN THE ETIOLOGY OF EACH AND THE TREATMENT MOST LIKELY TO BE EFFECTIVE

	Glossitis	*Diarrhea*	*Steatorrhea*	*Posterolateral column degeneration*	*Indirect reactive bilirubinemia*	*Deficiency*	*Treatment*
Pernicious anemia	+	±	−	+	+	Vitamin B_{12} conditioned by a deficiency of intrinsic factor	Vitamin B_{12} parenterally
Nutritional macrocytic anemia	+	+	−	±	−	Vitamin B_{12} and folic acid (dietary), the former deficiency predominating	Vitamin B_{12} or folic acid (oral or parenteral)
Sprue	+	+	+	±	−	Vitamin B_{12} and folic acid (dietary), the latter predominating. Exact etiology unknown	Folic acid (oral or parenteral). Vitamin B_{12} (parenteral)
Pernicious anemia of pregnancy	+	±	−	−	Rare	Folic acid co-enzyme due to metabolic abnormality + fetal demands	Folic acid
Megaloblastic anemia of infancy	+	±	−	−	−	Folic acid and ascorbic acid (dietary)	Folic acid and ascorbic acid
Refractory megaloblastic anemia	+	−	−	−	−	Folic acid co-enzyme due to metabolic abnormality	Folic acid
Megaloblastic anemia of scurvy	+	−	−	−	−	Ascorbic and folic acids (dietary)	Ascorbic acid and folic acid
Megaloblastic anemia due to intestinal blind pouches, etc.	+	−	−	±	±	Vitamin B_{12} due to abnormality of absorption induced by G.I. tract organisms	Folic acid, or parenteral vitamin B_{12}, aureomycin and surgery
Fish tapeworm anemia	+	−	−	±	±	Vitamin B_{12} deficiency due to metabolic activity of the worm	Vitamin B_{12} and vermifuge

All of these forms of anemia are characterized by megaloblastic maturation arrest in the bone marrow, macrocytic anemia, leucopenia, thrombopenia and old multilobed neutrophiles in the peripheral blood. Only patients with this type of anemia will respond to folic acid. There is no evidence that folic acid activates any other hematopoietic agent nor that it improves the absorption of vitamin B_{12} or iron, except in sprue.

The important clinical differences between these types of megaloblastic anemia are given in Table 30. There can be no objection to giving folic acid in addition to vitamin B_{12} to patients with pernicious anemia. Since this type of anemia is the result of a deficiency of intrinsic (gastric) factor which induces a deficiency in vitamin B_{12}, the latter substance is really all that is necessary for effective therapy. However, a vitamin B_{12} deficiency in some way seems to induce an abnormality in folic acid metabolism and there have been occasional patients with pernicious anemia who have responded at first to vitamin B_{12} and several years later have been found to be refractory to this substance, but responsive to folic acid.[53]

After folic acid is administered to a patient with pernicious anemia, reticulocytosis begins on the third day and usually is maximal on the eighth to tenth day. Frequently there is a secondary rise following the first peak. The reticulocyte peak is almost as high as might be expected when pernicious anemia is treated with vitamin B_{12} and the erythrocytes and hemoglobin return to normal in three to four weeks. It should be remembered however that if folic acid alone is used, the great majority of patients with pernicious anemia will develop serious perhaps permanently crippling peripheral neuritis, posterolateral column, cerebral or cerebellar degeneration or hematological relapse within a few weeks to three years.[54] The hematologic relapse usually occurs later than the neurologic. Mixed vitamin capsules containing folic acid as an ingredient may allow neurologic degeneration to occur while the anemia is kept in check.

Patients with sprue respond well to folic acid administered orally. Usually 15 mg daily in divided doses is sufficient. Glossitis begins to improve by the third or fourth day, reticulocytosis begins at this time and continues for many days. Seldom does one see the rapid rise and fall of reticulocytes that occurs when a patient with pernicious anemia is treated with vitamin B_{12}. Erythrocytes and hemoglobin increase, diarrhea abates, hypoprothrombinemia and carotene, vitamin A and calcium deficiencies are overcome. The deficiency pattern demonstrable in the gastroenteric tract by roentgen study improves or is entirely relieved. Glucose, carotene and vitamin F tolerance curves return to normal.[55] Usually a maintenance dose of 5 mg daily is required but occasionally a patient will continue in remission if he avoids fats and improves his diet by including meat, liver, green vegetables and fresh fruit, or lives on a gluten free diet.[55a]

Patients with primary disease of the small bowel such as idiopathic steatorrhea, celiac disease, regional ileitis, tuberculous enterocolitis or lipophagic granulomatosis (Whipple's disease) who develop macrocytic anemia may derive some improvement in the anemia from folic acid treatment but no definitive change in small bowel function occurs. The same statement holds for patients with macrocytic anemia associated with pancreatic steatorrhea.

Patients with nutritional macrocytic anemia and tropical macrocytic anemia will respond to 15 mg folic acid orally in divided doses each day. Glossitis clears, reticulocytosis begins on the third or fourth day and is maximal on the eighth to tenth day, falling slowly thereafter. Erythrocytes and hemoglobin increase to normal levels in three to four weeks. Remissions will be maintained without folic acid if the disease has not been present so long that irrevocable damage has been done to the gastrointestinal tract and if the patient makes every effort to eat an adequate diet.

Fifteen mg of folic acid is adequate also in patients with pernicious anemia of pregnancy. Maintenance therapy is not necessary between pregnancies but relapse may occur with subsequent pregnancies. The same dose is satisfactory in achrestic anemia and after remission has been induced maintenance of this remission will require 1 to 5 mg daily. Relapse tends to occur otherwise.

One to 5 mg daily given orally is highly effective therapy for megaloblastic anemia of infancy. No maintenance therapy is necessary. Any associated deficiency states accompanying these varieties of macrocytic anemia should be treated with the appropriate nutrient. Usually this type of supplemental therapy is necessary only at the beginning of the therapeutic program. In every instance, careful attention should be given to dietary improvement.

When fish tapeworm anemia is encountered folic acid or vitamin B_{12} will induce a hematologic response but the worm should be removed. Patients with gastrocolic fistulæ and intestinal blind pouches should have these defects rectified surgically after careful preparation with folic acid, vitamin B_{12}, other nutrients which the patient lacks, high protein diet and antibiotics. If the procedures are successful no maintenance therapy is usually needed. Postgastrectomy pernicious anemia should be treated with parenteral vitamin B_{12} as the usual case of pernicious anemia is treated.

Folinic acid is approximately as potent as folic acid in the conditions just described.[56] Its chief therapeutic value is in the reversal of aminopterin toxicity or overdosage in leukemic children who are receiving this antagonist. Three mg daily given parenterally should be sufficient to relieve the ulcerated mouth, throat and gums of aminopterin toxicity but it will also release the leukemic process from the brake imposed upon it by the folinic acid deficiency induced by aminopterin.

As yet an accurate estimate cannot be made of the daily requirement for the folic acid group in human beings. An average diet that will maintain good folic acid nutrition contains 0.5 to 1.0 mg and 1 mg daily will usually induce a hematopoietic response in a patient with pernicious anemia in relapse. However, the amounts of these substances obtained from the activity of the gastro-enteric tract organisms is quite unknown and probably varies under different dietary and environmental conditions. Furthermore the amounts of other essential nutrients in the diet probably alters the need for folic acid so that a minimal or optimal requirement cannot be set. It is probable that 0.5 to 1.0 mg daily will maintain good health under most conditions.

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VITAMIN B_{12}

By Richard W Vilter

Introduction—The recognition and isolation of vitamin B_{12} in the United States of America depended upon the fortunate discovery by Shorb[1] of a test organism, Lactobacillus lactis dorner, whose growth was proportional to the amount of antipernicious anemia factor in liver extract With the help of this tool, Rickes and his co-workers isolated vitamin B_{12} and West[3] demonstrated that it had antipernicious anemia activity Similar work was in progress in England at the same time and Smith[4] was able to isolate vitamin B_{12} from liver by clinical test in patients with pernicious anemia and by following the red color of the active material Vitamin B_{12} has been shown to be Minot's parenteral liver factor, the extrinsic factor of Castle and an animal protein factor, though other animal protein factors may exist

Chemistry of Vitamin B_{12}—Vitamin B_{12} is a red crystalline compound with a molecular weight of 1355 and the structural formula given below It is a cobalt-porphyrin benzimidazole ribofuranose phosphate (See Fig 26) The cobalt is linked coordinately to the benzimidazole moiety through one of the latter's nitrogen atoms This linkage is similar to that which binds iron to porphyrin in heme[5] A cyanide group is also linked to cobalt[5a]

Vitamin B_{12} may exist in several different forms which have been given the generic name cobalamine[6] Cobalamine behaves as a cation in aqueous solution and forms an un-ionized salt with cyanide, cyanocobalamine (vitamin B_{12}), with hydroxide, hydroxo-cobalamine (vitamin B_{12a} and vitamin B_{12b}), with nitrite, nitrito-cobalamine (vitamin B_{12c} and probably vitamin B_{12b}), and thiocyanate, thiocyanato cobalamine Ionized salts may be formed also, such as aquacobalamine sulfate and aquacobalamine chloride Cobalamine may combine also with ammonia and compounds containing amino groups such as histidine, peptides and proteins (cobalt

chromes) This may be the way vitamin B_{12} is bound in tissues Finally vitamin B_{12b} has been converted by micro organisms to compounds in which the benzimidazole is replaced by a purine base such as adenine (pseudovitamin B_{12} or vitamin B_{12f}) Cyanocobalamine hydroxocobalamine, nitrito cobalamine and thiocyanatocobalamine have similar activities in patients with pernicious anemia Pseudovitamin B_{12} and vitamin B_{12f} are inactive in this disease but are active for growth of microorganisms [7]

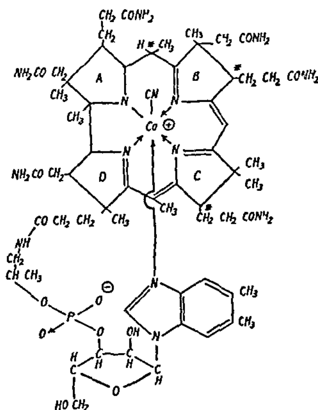


FIG 26 —The structural Formula of Vitamin B_{12}

Sources of Vitamin B_{12} —Much of the vitamin B_{12} in food occurs in the form of a protein complex Such bound forms are inactive for the growth of most microorganisms until the vitamin B_{12} moiety is released by proteolytic enzymes or heat Vitamin B_{12} is found almost exclusively in foods of animal origin It is synthesized by many bacteria among which streptomyces griseus, streptomyces aureofaciens and bacillus subtilis are common commercial sources Herbivorous animals obtain vitamin B_{12} from the micro-organisms in the rumen and it is probable that these organisms are the main sources of the B_{12} found in the animal kingdom

Determinations of the vitamin B_{12} activity in various foods has been hampered by difficulties with microbiological tests and by lack of complete correlation between activity for test organisms and activity in animals and in human beings with pernicious anemia

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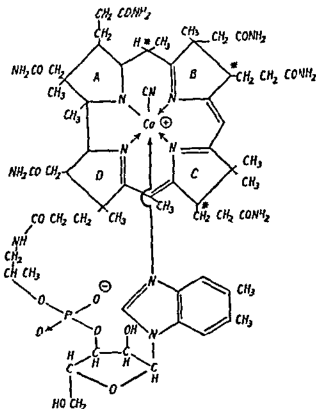


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Determinations of the vitamin B_{12} activity in various foods has been hampered by difficulties with microbiological tests and by lack of complete correlation between activity for test organisms and activity in animals and in human beings with pernicious anemia

In general, however, our best sources of vitamin B_{12} are liver, kidney meat, and milk listed in order of decreasing concentration of the vitamin (Table 31) Over 70 per cent of the vitamin B_{12} activity is retained during cooking

TABLE 31 —THE AMOUNT OF VITAMIN B_{12} IN VARIOUS FOODS
(mμg/gm or ml)

Beef liver	310 0–1200†
Beef kidney	180–550†
Lamb leg	17–66†
Beef round	34–45†
Ham	9–16†
Milk, cow	1 6–6 6*
Sheep	1 4*
Goat	0 12*
Human	0 41*
Oats	3 0‡
Soybean meal	2 0‡
Wheat	1 0‡
Brewers yeast	1 0‡
Yellow corn	0 0‡

* (Reference 61)
‡ (Reference 62)
† (References 63 and 64)

Physiology of Vitamin B_{12} —Vitamin B_{12}, released from its combination with food protein in the stomach and upper gastro-enteric tract, is very poorly absorbed by human beings unless a heat labile protein enzyme, the intrinsic factor, is present at the same time This factor, which is produced by the fundal and cardiac glands of the stomach and is found in abundance in normal human gastric juice either protects the vitamin from absorption or destruction by bacteria in the upper gastro-enteric tract, or facilitates the passage of the vitamin across the intestinal mucous membrane [8] The intrinsic factor has been concentrated from hog gastric mucous membrane and is available commercially It is a mucoprotein or a mixture of mucoproteins Vitamin B_{12} is bound by it, but the degree of intrinsic factor activity is not proportional to the degree of binding [10] Intrinsic factor preparations have a high degree of species specificity [10a] For instance hog or human intrinsic factor decrease the vitamin B_{12} absorption by rats, though rat intrinsic factor or stomach mucosa has a potentiating effect It is fortunate that hog and human intrinsic factor preparations have similar activity in human beings, though the hog preparation contains an inhibitor of vitamin B_{12} absorption for the human being which can be recognized when large doses are given [10b] Binding sites on intrinsic factor can be blocked by vitamin B_{12} analogues [10c]

Vitamin B_{12} given in large doses can be absorbed by the intestine without the intermediation of intrinsic factor [10d] It is only when persons are given doses of the order contained in ordinary foodstuffs that intrinsic factor plays a role in absorption There is evidence that intrinsic factor helps to bind vitamin B_{12} to the intestinal mucosa [10e] There still is disagreement about the portion of the ileum where vitamin B_{12} is absorbed

Patients with pernicious anemia develop their disease because their meager gastric secretions are very deficient in intrinsic factor. This defect results in a serious deficiency in vitamin B_{12}. It is a gene linked abnormality.

After absorption, vitamin B_{12} is bound by proteins in the plasma[11] and circulates to the various sites of its metabolic activity. That portion which is not bound is thought to be excreted rapidly by the kidney. Horrigan and Heinle[12] have suggested that lack of proper B_{12} binding proteins in the plasma may result in a B_{12} deficiency state. Most of the vitamin B_{12} absorbed by the body is stored in the liver, apparently in combination with protein. Exactly how this storage is accomplished is not known but *in vitro* studies indicate that the uptake of vitamin B_{12} by liver slices is increased by the presence of intrinsic factor. The increment in uptake is directly proportional to the activity of the intrinsic factor preparation. This property has been suggested as a test for intrinsic factor activity.[12a]

TABLE 32.—THE VITAMIN B_{12} CONTENT OF SERUM FROM NORMAL PERSONS AND PATIENTS WITH PERNICIOUS ANEMIA IN RELAPSE
($\mu\mu g$/ml)

	EUGLENA GRACILIS					L. LEICHMANNII
	Mollin & Ross[13]		*Lear et al.*[14]		*Pitney & Beard*[15]	*Unglaub et al.*[14b]
	Total	*Combined*	*Total*	*Free*	*Total*	*Total*
Normal	100–720	100–620	292–856	27–104	86–460	70–420
P. A. in Relapse	<16–105	<16–105	0–85	0	20	10–70

Normal plasma vitamin B_{12} levels determined by the Euglena Gracilis method vary greatly and are given in Table 32. Plasma levels in patients with pernicious anemia are about one-tenth of the normal level in each series. Very high serum levels have been found in patients with cirrhosis and myeloid leukemia. In aged persons serum vitamin B_{12} levels are somewhat lower than normal and such persons do not absorb the vitamin as well as younger subjects.[1b] Little vitamin B_{12} activity (in the range of 0.10 to 0.25 μg/twenty four hours) can be measured in the urine even in a normal person given 1 to 3 mg. by mouth. In patients with pernicious anemia the urine levels in one series are even lower, in the range of 0.02 to 0.15 μg/twenty four hours.[13] In another series the urine levels are essentially the same for both normal persons and pernicious anemia patients: 0.041 ± 0.006 μg/twenty four hours for the normal group and 0.065 ±0.013 μg/twenty-four hours for the pernicious anemia group.[14a] The stool contains a large amount of B_{12} activity (in the range of 5 μg/twenty-four hours) arising in large measure from the micro-organisms of the gastro-intestinal tract.[15] Since it has been shown that little vitamin B_{12} can be absorbed from the colon, it is probable that little of the vitamin derived from gastro-intestinal tract organisms is available to the human host. If this source of material were available to the patient with pernicious anemia, he would never develop his disease.

Vitamin B_{12}, administered parenterally, circulates in the blood and is excreted in the urine in amounts proportional to the size of the dose injected.[16,17] Most of a 40 µg dose is retained. As this upper limit is exceeded, there is greater and greater loss in the urine until with a dose of 210 µg, 68 per cent is lost in eighteen hours and with a dose of 1000 µg, 95 per cent is lost in the same length of time.

Saliva binds vitamin B_{12} but does not facilitate absorption.[19] Rectally administered vitamin B_{12} is poorly absorbed.[20] However, good absorption occurs when it is given in an aerosol by inhalation.[21]

In animals, the injected vitamin is sequestered in the following organs, listed in order of decreasing concentration: Kidney, muscle, liver, pancreas, skin, testes, blood, brain, heart, spleen, bone marrow.[22] No new physiologic properties are conferred upon vitamin B_{12} through the mediation of the intrinsic factor or by the binding proteins of the plasma after parenteral administration. It may be injected directly into one iliac crest marrow cavity of a patient with pernicious anemia in relapse and if the dose is properly selected, it will exert a local maturation effect without inducing a systemic response.[1] Undoubtedly vitamin B_{12} binding proteins and enzyme systems in the deficient cells of the pernicious anemia marrow hold the vitamin at the site of injection unless a large dose is given.

Though only minute amounts of vitamin B_{12} are present in the tissues of animals and man these small quantities are held with great avidity. Vitamin B_{12}-deficient female rats are often used for breeding purposes in order to be certain of vitamin B_{12}-deficiency manifestations in the offspring.[24] Human beings with pernicious anemia treated with liver extract (containing vitamin B_{12}) or the crystalline vitamin usually do not suffer a relapse for six months to seven or more years after treatment is discontinued. Likewise a lapse of three to five years usually occurs between total gastrectomy in human beings and the appearance of megaloblastic anemia.

Metabolic Functions of Vitamin B_{12}.—In the cells vitamin B_{12} is found in the mitochondria[5] where it plays a very important catalytic role. Some general observations have been made on the effect of vitamin B_{12} on metabolic processes in laboratory animals. As the protein content of the diet is increased the vitamin B_{12} requirement increases suggesting a relationship to protein metabolism.[6] Serine and glucose are incorporated into liver protein to a lesser extent in vitamin B_{12} deficient animals than in those that have an adequate supply of the vitamin.[6a] Perhaps an activated vitamin B_{12}—protein serves as a carrier for amino acids during protein synthesis. A relationship to fat metabolism has been suggested by the observation that the carcasses of vitamin B_{12} deficient rats contain much less fat than the vitamin B_{12} treated counterparts.[7] Carbohydrate metabolism may be dependent upon vitamin B_{12} also.[8]

The exact metabolic role played by vitamin B_{12} is not known. A vitamin B_{12} coenzyme has been discovered. Many rather specific functions for the vitamin have been proposed. These include transmethylation, i.e., the transfer of methyl groups from methionine to ethanolamine to form choline; methyl biosynthesis such as the formation of a methyl group from glycine, serine or formate; disulfide reduction to the sulfhydryl radicle and other reduction reactions such as the conversion of the methyl hydroxy

group to the methyl group, perhaps while such groups are attached to tetrahydrofolic acid. This type of reaction may activate the folic acid coenzyme. Vitamin B_{12} is involved directly or indirectly in purine-pyrimidine nucleoside biosynthesis.[7, 9a, 28b, 8]

Evidence has been obtained from laboratory animal studies and experiments with bacterial growth and tissue slice metabolism to support each of these functions. At the present time however it is the consensus of most investigators in this field that transmethylation is affected by vitamin B_{12} only indirectly if at all. In the young pig and other laboratory animals Johnson was unable to demonstrate any effect of vitamin B_{12} on a number of transmethylation reactions.[29] He and many others have been able to show a direct effect of vitamin B_{12} on methyl biosynthesis in baby pigs, chicks and rats.[9] A sparing effect by vitamin B_{12} of methyl groups was demonstrated soon after the vitamin was discovered.[96] Cell free extracts from B coli derive methyl groups from serine in the presence of vitamin B_{12}.[9]

Dubnoff has demonstrated an effect of vitamin B_{12} on the maintainance of sulfhydryl (SH) groups in the reduced state.[30] Since many important enzyme systems contain sulfhydryl groups this could be a major metabolic role for the vitamin. The suggestion has been made that homocystine must be reduced to homocysteine before a methyl group can be added to form methionine and that vitamin B_{12} facilitates this reaction. Johnson was unable to substantiate this however.[29] There is also a hypothesis that vitamin B_{12} activates the folic acid coenzyme and thereby controls those reactions dependent upon folic acid.[7, 30a, 4] (See section on Folic Acid.) Direct evidence favoring this role has been obtained from experiments with cell free systems and indirect evidence along the same lines has been marshalled from studies on patients with pernicious anemia in relapse. Such an effect probably depends upon the reduction activity of vitamin B_{12} possibly at the stage of hydroxymethyl or formyl tetrahydrofolic acid reduction. Vitamin B_{12} may also effect the release of folic acid from its conjugated form by activating a sulphydryl containing enzyme system (a conjugase). By any of these mechanisms a patient with pernicious anemia deficient in vitamin B_{12} might become deficient in the folic acid coenzyme. Such a secondary deficiency state could explain why such patients respond temporarily to folic acid administration.

Vitamin B_{12} is also implicated in the formation of purine and pyrimidine ribosides and deoxyribosides. Such a function involves the vitamin in nucleic acid metabolism. Thymidine and other pyrimidine deoxyribosides will replace vitamin B_{12} as growth factors for lactobacillus leichmannii and streptococcus faecalis when purines are available.[31] C^{14} thymidine labels all nucleosides in L leichmannii when this organism is grown on a medium containing it but the specific activity of the label is reduced when B_{12} is added also.[31] These results are interpreted to reflect a greater dilution of the added C^{14} nucleoside as a result of greater nucleoside synthesis when vitamin B_{12} is present in the medium. Since all deoxynucleosides will replace vitamin B_{12} for growth of L leichmannii the suggestion has been made but not proved that the vitamin functions in the synthesis or utilization of deoxyribose or in nucleoside interconversions.

A relationship of vitamin B_{12} to pyrimidine metabolism either directly or by activation of the folic acid coenzyme is suggested by the hematologic responses of patients with pernicious anemia to thymine, uracil, and orotic acid.[32,33,33a] Furthermore, bone marrow cells of patients with pernicious anemia contain much more uracil and ribose nucleic acid before treatment with hematopoietic vitamins, such as vitamin B_{12} and folic acid, than afterwards when these values reach normal levels. Thymine and deoxyribose nucleic acid do not change significantly.[34,34a] These chemical observations may be explained by the following hypothesis. Vitamin B_{12} deficient (and therefore folic acid deficient) bone marrow cells cannot synthesize deoxyribose nucleic acid containing thymine, and therefore marrow mitotic activity decreases. In the resting stage these cells, the megaloblasts, continue to synthesize some ribose nucleic acid and protein.[34b] They grow large, and the nucleus appears to be very young in comparison with the cytoplasm but contains a normal amount of deoxyribose nucleic acid. This is essential for viability. Only when cells enter the prophase of mitosis does the deoxyribose nucleic acid change. An increase occurs at this stage. When necessary precursors for thymine nucleoside synthesis are furnished either directly as the pyrimidine moiety or through use of the hematopoietic vitamins, the nucleus can build up deoxyribose nucleic acid for mitosis, maturation is resumed and ribose nucleic acid decreases. As its metabolism is corrected the megaloblast becomes a normoblast.

Vitamin B_{12} has been linked also to the formation of RNA. It has been shown to be important for the maintainance of RNA in the livers of rats poisoned with carbon tetrachloride and in the cells of the central nervous system of laboratory animals.[3,36] From such data, one may deduce that vitamin B_{12} is involved in the formation and degradation of both ribose nucleic acid containing uracil and deoxyribose nucleic acid containing thymine. Related enzyme systems probably determine in which direction these reactions go since they are certainly reversible. So in one tissue the emphasis may be placed on the formation of deoxyribose nucleic acid and the degradation of ribose nucleic acid, while in another tissue, the reverse effect may be observed.

A discordant note must be sounded at this point. In spite of all this evidence implicating vitamin B_{12} in nucleic acid metabolism, Johnson was unable to confirm such a role for vitamin B_{12} in the baby pig, chick, or rat. He was able, however, to demonstrate greater labeling of uric acid in vitamin B_{12} treated chicks than in deficient birds after the administration of C^{14} labeled glycine, serine, formate, and methionine.[29] These results suggest that the effects of vitamin B_{12} on purine, pyrimidine and nucleic acid metabolism previously reported are indirect, and are mediated through an effect of vitamin B_{12} on other catalysts such as the folic acid coenzymes.

Vitamin B_{12} may be measured in biological material by the growth responses of Lactobacillus lactis dorner ATCC8000[37] and Lactobacillus leischmannii ATCC4797 or ATCC7830.[38] When either of these organisms is used, thymidine will interfere with the test. Euglena gracilis var. bacillaris[39] is more sensitive to stimulation by vitamin B_{12} than are the organisms previously mentioned. E. gracilis is not responsive to purines or pyrimidines and therefore these substances do not interfere with the tests.

Ochromonas malhamensis and mutant forms of E. coli have been used to estimate vitamin B_{12} levels also.[39a] A chemical method dependent upon liberation of cyanide from cyanocobalamine is available[40] but is less adaptable than the microbiologic methods and has not been used extensively.

Radioactive cobalt$_{60}$[41] has been incorporated into vitamin B_{12} and this material has been used quite successfully in tracer studies.[4] With it, the defect in vitamin B_{12} absorption in patients with pernicious anemia has been clearly demonstrated, and tests for intrinsic factor activity have been developed. Patients with treated or untreated pernicious anemia may be used in these tests. Five-tenths μg vitamin B_{12} Co$_{60}$ is given by mouth with or without intrinsic factor. When no intrinsic factor is given, 80 to 90 per cent of the radioactivity appears in the stool. When a potent intrinsic factor is included, only 20 to 25 per cent appears in the stool. If a parenteral dose of 1000 μg vitamin B_{12} is given one hour after the oral dose, the amount of radioactivity flushed out in the urine may be used as a measure of vitamin B_{12} absorption.[43] Labelled vitamin B_{12} has been used also for the determination of the organs in which injected or orally administered vitamin B_{12} is stored,[41] and the hepatic uptake of the labeled vitamin as determined by surface counting has been used to estimate vitamin B_{12} absorption.[43a]

Vitamin B_{12} Deficiency States in Human Beings.—Pernicious anemia occurs when vitamin B_{12} is not available to the human being who lacks intrinsic factor in his gastric secretions. The origin of the gastric defect is unknown but is under genetic control. Atrophic gastritis is associated with this defect and the gastric mucosal cells are morphologically abnormal. The vitamin B_{12} deficiency that ensues probably causes metabolic abnormalities in the activity of related enzyme systems. There is some evidence that in this fashion the normal metabolism of folic acid is deranged and secondary or tertiary deficiency states are induced.[39a, 44, 4] The comm[illegible] manifestations of this disease are listed in the order that they usu[illegible] appear: (1) inflammation followed by atrophy of the tongue, oral [illegible] and other mucous membranes of the gastroenteric tract, (2) ma[illegible] anemia, megaloblastic bone marrow and (3) degeneration of the [illegible] nerves, the posterior and lateral columns of the spinal cord, [illegible] brum and cerebellum. Erythrocytes, white blood cells and [illegible] formed at slow rates. Erythrocytes grow large and have [illegible] normal life span (about sixty days rather than one hun[illegible] days). Transfused red blood cells may be destroyed [illegible] As a result, indirect reacting serum bilirubin is ele[illegible] histamine refractory achlorhydria and many other [illegible]ities such as negative nitrogen balance, decreas[illegible] in erythrocytes and plasma, moderate h[illegible]remia, slightly lowered erythrocyte protopor[illegible] acid and cholesterol levels. The metabolism of ty[illegible] indicated by increase in total phenolic compounds in t[illegible] These abnormalities except the achlorhydria, gastric atrop[illegible] cell metapl[illegible] and achylia gastrica are reversed by [illegible] of vitamin [illegible] parenterally in small doses or orally [illegible] in conjunct[illegible] intrinsic factor. The parenteral [illegible] B_{12} required [illegible]

ment of pernicious anemia in relapse is 1 microgram daily. Usually, however, 10 to 15 micrograms daily are given. Fifty to 100 micrograms daily have been advocated in patients with posterolateral column degeneration or with active infections or severe arteriosclerosis. Remissions can be maintained with 15 to 30 micrograms every three to four weeks. If the vitamin is given by the oral route, unpredictable responses may be obtained with doses ranging from 5 to 3000 micrograms daily. Adequate maintenance for a year has been attained with an oral dose of 1 mg weekly.[50] When intrinsic factor and vitamin B_{12} are combined in 1 tablet, the dose is usually quoted in units, 1 unit being that amount of combined material which when given daily to a patient with pernicious anemia in relapse, will induce a complete remission. Even though these materials are available it is safer and cheaper to rely on the parenteral route for both treatment and maintenance of patients with pernicious anemia.

All attempts to induce a comparable syndrome in laboratory animals by restriction of vitamin B_{12} intake have failed. Only a mild normocytic normochromic anemia responsive to vitamin B_{12} has occurred.[51,52] A blood and bone marrow picture more closely resembling that seen in pernicious anemia has been induced in swine by administration of a folic acid antagonist and a diet deficient in both folic acid and vitamin B_{12}.[53,54] These animals may respond temporarily to vitamin B_{12} but require folic acid for a complete response.

Combined dietary deficiencies of vitamin B_{12} and folic acid in human beings result in megaloblastic anemia morphologically similar to pernicious anemia. However, achlorhydria, achylia gastrica, neurologic manifestations and jaundice are usually lacking. Vitamin B_{12} 10 to 15 micrograms[5] or folic acid 10 to 15 milligrams given orally or parenterally will usually induce a favorable therapeutic response, and a diet high in animal protein usually will maintain this remission. This type of anemia has been called nutritional macrocytic anemia.

Sprue is a malabsorption syndrome of dietary origin in the etiology of which folic acid and vitamin B_{12} deficiencies play prominent roles. Patients with this disease will respond to larger parenteral doses of vitamin B_{12} (25 to 50 micrograms daily)[56] than are usually necessary in the treatment of pernicious anemia. Folic acid is preferred therapy, however. Even though there is improvement in the diet, folic acid or vitamin B_{12} usually must be continued to maintain the patient in good health. Except for the fish tapeworm anemia and post-gastrectomy pernicious anemia other forms of megaloblastic anemia usually do not respond to vitamin B_{12}. These are megaloblastic anemia of infancy, pernicious anemia of pregnancy, and vitamin B_{12} refractory megaloblastic anemia (achrestic anemia). They respond to folic acid.

Vitamin B_{12} has been used empirically and frequently without much experimental or theoretical justification in many different conditions, all unrelated to megaloblastic anemia. Wetzel[57] and others[58] have gathered data which suggest that this vitamin stimulates growth in chronically malnourished children. Gains in appetite and weight have been reported. Other investigators have not been able to confirm their claims.[59,60] Nutritional neuritis, diabetic neuritis and tic douloureaux have been said to re-

spond, particularly to doses of 1000 micrograms daily [60] It has been used in these large doses in other painful afflictions and in diabetic neuroretinopathy with even less justification up to the present time One finds it hard to understand how such large parenteral doses of vitamin B_{12} can be effective when 95 per cent of the vitamin is lost in the urine within a few hours

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VITAMIN C (ASCORBIC ACID)

By Richard W Vilter

In 1928 Szent-Gyorgyi[1] isolated hexuronic acid from orange juice, cabbage juice and ox adrenal glands In the same year Waugh and King showed that it was identical to an antiscorbutic substance, vitamin C, which they had isolated from lemon juice Haworth[3] determined its structure and Reichstein[4] synthesized it The search for the antiscorbutic vitamin had reached a successful conclusion Scurvy, a disease caused by lack of this substance, had been recognized and clearly described in the Ebers Papyrus, discovered at Thebes and written about 1500 B C[5,6]

Hopkins suggested that infantile scurvy, similar to scurvy in adults, was a deficiency disease in 1906[7] and in 1907, the disease was reproduced in animals by Holst and Frolich[8] During the second decade of the 20th century, Zilva and his co-workers began the early work which ultimately led to the isolation and synthesis of vitamin C[9] They showed, in animals that the teeth are affected early in the course of the disease In 1926 Wolbach and Howe[10,11] recognized that failure of formation of intracellular cement substance was one of the fundamental pathologic abnormalities in guinea pig scurvy Thereafter the vitamin was isolated defined as to structure and synthesized Thus many centuries elapsed between the recognition and description of scurvy, the description of methods of cure and the isolation and synthesis of the curative principle vitamin C

Distribution of Ascorbic Acid in Food —The only significant dietary sources of ascorbic acid are fruits vegetables and liver Meats, cereals and dairy products contain such small amounts that they are of little importance as antiscorbutic foods Citrus fruits and fresh tomatoes provide the most reliable dietary sources though it is seldom realized that other vegetables in the freshly harvested state contain relatively more of this vitamin However, storage and processing methods usually reduce the vitamin C content of these vegetables before they reach the table and if these methods have been particularly poor the foods originally rich in the essential nutrient may contribute little or no vitamin C to the diet

Green leaves of spinach or lettuce have lost most of a high vitamin C content after wilting for several days at room temperature Root vegetables tightly packed leaves of cabbage and hard fruit lose vitamin C very slowly Fifteen per cent of the original vitamin C content may remain after storage for six or more months Low temperature protects the vitamin

Processing procedures have various effects on the vitamin C content of vegetables Boiling leaches out this water soluble substance but, if heat has rapidly inactivated the oxidase systems and air is excluded little is destroyed Steaming leaches out little vitamin but allows oxidation to proceed more rapidly Pressure cooking for short periods of time results in relatively greater oxidation than leaching Each method of cooking if done only to the point of palatability of the vegetable preserves about the same amount of the vitamin in the final product—roughly 50 per cent

Steam table warming, a favorite restaurant procedure, destroys all remaining vitamin C very rapidly

Freezing and storage of blanched vegetables below −20° C preserves vitamin C However, there are some losses during the blanching process and considerably more if the thawed vegetable is not cooked and served immediately

Dehydration of fruits by modern methods causes only very small losses and, if stored in an atmosphere free of oxygen, foods so prepared keep their ascorbic acid content almost indefinitely Modern methods of canning also tend to preserve the ascorbic acid content of food and, though there are some losses during the process of blanching, heating in the tins, and after standing on the store shelves, the final content when served is about the same as if the fresh vegetable had been cooked on the kitchen stove for the longer time required to make it palatable

Other sources of vitamin C have been discovered due to the scarcity of citrus fruits and fresh vegetables in Europe during World War II Green walnuts, rose hips, pine needles and guava provide excellent sources which could be used in an emergency For more details, the reader is referred to a recent monograph on this subject [1] Table 33[13] lists the vitamin C content of those foods which are richest in this substance

TABLE 33 —ASCORBIC ACID CONTENT OF FOODS RICH IN THIS VITAMIN

Food	*Ascorbic acid (mg /100 gm)*	*Food*	*Ascorbic acid (mg /100 gm)*
Apple		Blackberries	
raw	5	raw	21
dehydrated	12	Blueberries	
cooked	1	raw	16
Apricots		Broccoli	
raw	7	raw	118
canned	4	cooked	74
Asparagus		frozen	75
raw	33	Brussels Sprouts	
cooked	23	raw	94
canned	15–88	cooked	47
Avocados	16	frozen	63
Bananas	10	Cabbage	
Lima Beans		raw	50
raw	32	cooked	31
cooked	15	Cantaloupes	33
canned	8	Cauliflower	
frozen	17	raw	69
Snap Beans		cooked	28
raw	19	frozen	51
cooked	14	Swiss Chard	
Wax Beans		raw	38
raw	19	cooked	17
canned	4	Collards	
Beets		raw	100
raw	10	cooked	44
cooked	7	Water Cress	
Beet Greens		raw	77
raw	34	Currants	
cooked	15	raw	36

Food	*Ascorbic acid (mg/100 gm.)*
Dandelion Greens	
raw	36
Endive	
raw	11
Grapefruit	
raw	40
canned	30
Guavas	302
Honeydew Melon	23
Kale	
raw	115
cooked	51
frozen	47
Kohlrabi	
raw	61
cooked	37
Lemons	
raw	50
canned juice	50
Lettuce	
headed	8
leaf	18
Limes	27
Liver	
raw	31
cooked	31
Loganberries	
raw	24
Mangos	
raw	41
Mustard Greens	
raw	102
cooked	45
Okra	
raw	30
cooked	20
Onions	
raw and green	24
Oranges	49
Orange Juice	
fresh	49
canned	42
frozen concentrate	141
Parsley	193
Peas	
raw	26
cooked	15
frozen	18
Peppers (Green)	
raw	120
cooked	99
Pimentos	
canned	95
Pineapple	
raw	24
canned	9
Potatoes	
raw	17
baked	17
boiled	15
Radishes	
raw	24
Raspberries	
raw	24
Rutabagas	
raw	36
cooked	21
Spinach	
raw	59
cooked	30
frozen	38
Squash	
raw	17
cooked	11
Sweet Potatoes	
raw	22
baked	23
Tangerines	31
Tomatoes	
raw	23
canned	16
Tomato Juice	
canned	16
Turnips	
raw	28
cooked	18
Turnip Greens	
raw	136
cooked	60

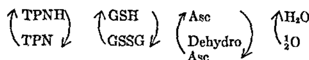
Chemistry and Pharmacology.—Vitamin C is a white odorless crystalline acidic substance with molecular weight of 176.06, melting point of 192° F, empiric formula of $C_6H_8O_6$ and the following structural formula

```
   O=C———┐
     |   |
  HO—C   |
     ‖   O
  HO—C   |
     |   |
   H—C———┘
     |
  HO—C—H
     |
    CH2OH
```

Ascorbic acid is an acceptable synonym It is quite soluble in water to the extent of 1 gm in 3 cc and to a lesser extent in alcohol and glycerine It is insoluble in benzene, chloroform, ether, petroleum ether or fat In solution, it is heat labile but in the dry state in air it is reasonably stable

The 1-isomer is the physiologically active form The first oxidation product is dehydroascorbic acid which also has antiscorbutic properties The latter compound is converted rapidly to 2-3 diketo-gulonic acid and to oxalic and 1-threonic acids at a *p*H greater than 4 In animal and plant tissues, copper and iron salts, hemochromagens and quinone catalyze the oxidation of ascorbic acid to dehydroascorbic acid In addition ascorbic oxidase,* polyphenol oxidase, cytochrome oxidase, and peroxidase systems also catalyze this reaction enzymatically

The conversion of dehydroascorbic acid to ascorbic acid is facilitated in animal and plant tissues by reduced di and tri phosphopyridine nucleotides and related enzyme systems, by way of glutathione and other compounds containing the SH group



TPN = oxidized triphosphopyridine nucleotide
TPHN = reduced TPN
GSSG = oxidized glutathione
GSH = reduced glutathione
Asc = ascorbic acid
Dehydro Asc = dehydroascorbic acid

Though the reaction indicated above is said to be irreversibly to the right, it is possible that quinones may act as hydrogen acceptors during an oxidation phase and split products of hexosediphosphate, malate, and isocitrate may act as hydrogen donors during the reduction phase In this way ascorbic acid may be involved in an important hydrogen transfer system and may regulate oxidation-reduction potentials within the cells For more details the reader is referred to a recent review of this subject [14,15]

In addition, ascorbic acid is important in the oxidation of l-tyrosine and phenylalanine[16] and appears to function as a co-enzyme in these reactions [17] In the absence of this vitamin para-hydroxy phenylpyruvic acid and para-hydroxy phenyllactic acid are excreted in the urine These are products of the incomplete oxidation of the phenolic amino acids It is essential also for the conversion of folic acid to folinic acid,[18] a reduction reaction, and it may play a part in the release of free folic acid from the folic acid conjugates found in food

Ascorbic acid has been related to the activity of many other enzyme systems but these claims have not been fully substantiated Its relationship to carbohydrate metabolism and the diabetogenic affect of dehydro ascorbic acid are still hypothetical [19] Thus, the specific chemical effects of ascorbic acid in cellular metabolism are not yet clearly defined though they are certainly of the oxidation-reduction type

* Not found in animal tissue

In human beings,[20] as in animals, ascorbic acid is nontoxic within very wide dosage limits. One thousand mg daily for three months had no deleterious effect on the clinical condition nor on the serum or buffy coat ascorbic acid levels or on tolerance tests. After either oral or parenteral administration, ascorbic acid is excreted rapidly in the urine when the tissues are saturated with it. It appears in the glomerular filtrate and is reabsorbed by the tubules. Tm for the tubules is reported to be 1.2 to 2.1 mg./100 cc. of glomerular filtrate. The renal threshold is 1.4 mg. per cent in the plasma.[12] This threshold falls as a state of deficiency progresses. There is always some vitamin cleared by the tubules even when the tissues are badly depleted. Under these circumstances less than 5 per cent of a test dose of 100 mg. given intravenously will appear in the urine within a period of three hours. When this same dose is given to a person whose tissues are saturated, more than 50 per cent will appear in the urine in this length of time.

Even when large doses of ascorbic acid are fed to human beings, only 6 to 10 mg. will appear in the stool in a twenty four-hour period.[23] Diarrhea will increase the loss by the anal route.

The highest concentrations of ascorbic acid are found in tissues of the highest metabolic activity, namely, in the retina and in decreasing concentration in the following tissues: pituitary gland, corpus luteum, adrenal cortex, thymus, liver, brain, testes, ovaries, spleen, thyroid, pancreas, salivary glands, lungs, kidney, intestinal wall, heart muscle, spinal fluid, white blood cells, erythrocytes and plasma.[24]

Estimation of Ascorbic Acid and Its Metabolites.—The most satisfactory reagent for the determination of the reduced ascorbic acid content of extracts of animal or vegetable origin is 2,6-dichlorophenol indophenol. For blood serum, for whole blood, and for the buffy coat ascorbic acid content, the methods are discussed in Chapter 17, page 497.

Human Requirements and Factors Influencing These Requirements.—The allowances for vitamin C recommended by the Food and Nutrition Board of the National Research Council are given in Table 34.

TABLE 34.—FOOD AND NUTRITION BOARD, NATIONAL RESEARCH COUNCIL RECOMMENDED DAILY DIETARY ALLOWANCES, REVISED 1958
Designed for the Maintenance of Good Nutrition of Healthy Persons in the United States of America

		Ascorbic Acid (mg.)
Men—all ages		75
Women—all ages		70
Pregnant (3rd trimester)	100	
Lactating (850 ml. daily)	150	
Infants —up to 1 year		30
Children— 1–3 years		35
4–6 years		50
7–9 years		60
Boys—10–12 years		75
13–15 years		90
16–20 years		100
Girls—10–12 years		75
13–15 years		80
16–20 years		80

These are the amounts necessary to maintain high vitamin C levels—tissue and plasma levels of 0 8 to 1 mg per cent without excessive loss in the urine Work in the United States of America and in other countries indicates that as little as 18 to 25 mg daily will prevent scurvy and keep the tissues half saturated, and 40 mg daily will prevent serious tissue depletion from a saturation level [5–8] The League of Nations Technical Commission on Nutrition (1938) and the Vitamin C Subcommittee of the British Medical Research Council (1948) recommended 30 mg daily [29] Ten mg daily is sufficient, in fact, to prevent scurvy for one year and maintain good healing properties of tissues even though the plasma ascorbic acid levels are 0 and the buffy coat levels almost 0 These data do not suggest that optimal nutrition is maintained by these low levels of intake They merely indicate that during periods of deprivation, disease may be prevented by much lower levels than those usually considered optimal On the other hand it is questionable whether health is greatly improved by an intake of 80 mg rather than 40 mg, though there is some evidence from investigations on animals that reproduction is improved and that other vital functions are more efficient [30]

An intake of 100 mg daily produces the maximal level of ascorbic acid in the plasma of fasting persons (1 12 mg) and minimal loss in the urine (20 mg)[31] Eighty to 100 mg of ascorbic acid daily will saturate the tissues (buffy coat levels of 24 2 mg per cent), and maintain a high serum level (0 8 mg per cent) [3]

Many factors increase requirements for ascorbic acid Recovery from scurvy seems to do this at least temporarily Pregnancy, lactation and thyrotoxicosis increase the amount of the vitamin required each day Diarrhea increases fecal losses, and achlorhydria decreases the amount of the vitamin absorbed before it is changed chemically to inactive substances

Other factors tend to decrease plasma levels Chronic inflammatory diseases and acute and chronic infection sidetrack the vitamin from the plasma to storage depots in the tissues Surgical operations and burns have the same effect but to an even greater degree Cold atmosphere increases the urinary excretion of ascorbic acid and dehydroascorbic acid but administration of the vitamin does not hasten adaptation to cold [32] In general the same circumstances that increase the need for other vitamins, or sidetrack them from the plasma have a similar effect on ascorbic acid

Pathology and Pathologic Physiology —The pathologic effects of ascorbic acid deficiency are most apparent in structures of mesenchymal origin newly formed fibrous tissue teeth, growing bones and blood vessels [11 33 34] These changes are the ones which account for the gross abnormalities which appear when human beings other primates and guinea pigs are deprived of dietary ascorbic acid Other animals synthesize the vitamin and therefore are not dependent on exogenous sources They accomplish the conversion of glucose to ascorbic acid by the following reactions D-glucuronate $\overset{TPNH}{\rightleftarrows}$ L-gulonate $\overset{DPN}{\rightleftarrows}$ (3 keto-L-gulonate)$\rightarrow$ L-ascorbate Human beings lack the enzyme system necessary for the conversion of 3 keto-L-gulonate to L-ascorbate [34a]

In connective tissue the young fibroblast lies in an amorphous ground substance in which fibrils are formed This ground substance, presumably produced by the fibroblast, cements the fibrils together and ultimately they are converted into wavy bands of collagen In ascorbic acid deficiency the ground substance or matrix is defective, and connective tissue or fibrous tissue scar does not form normally Wounds do not knit together firmly and therefore tend to break down This ground substance is thought to be composed of mucopolysaccharides

It is interesting to note that during the normal process of wound healing and production of new connective tissue ascorbic acid appears in very high concentration in the wound area In depleted subjects and persons with scurvy, whose wounds fail to heal, little or no ascorbic acid is found in the area and fibroblasts fail to grow into the blood clot at the base of the wound [35] Therefore wounds fail to heal and tensile strength of the scar is reduced [29 35–37]

A similar abnormality occurs in growing bone of scorbutic children In this instance the bone matrix, ground substance or osteoid is defective When nutrition is normal, two zones of ossification appear in the cartilage at each end of the growing long bone One is in the epiphysis and the other at the end of the diaphysis In the diaphyseal region the cartilaginous cells nearest the shaft of the bone line up in columns and begin to degenerate while the *cartilaginous matrix is calcified* Blood vessels and connective tissue from the bone marrow of the shaft invade this area (area of provisional calcification) penetrate the cartilaginous columns and destroy the cartilage cells Some of the fibroblasts become osteoblasts and line the walls of the columns The interstitial calcified cartilage between the columns is dissolved and new matrix is laid down by the osteoblasts This material is rapidly ossified to form the trabeculae of new bone The epiphyseal center of ossification progresses in the same fashion

In ascorbic acid deficiency calcification is not impeded and the zone of provisional calcification forms normally and may become even denser than usual because of the slow growth of the cartilaginous columns At this point the abnormalities in connective tissue appear Fibroblasts do not become osteoblasts Instead they migrate back into the shaft of the bone What little matrix they produce does not gel and appears like loose connective tissue It is so abnormal that ossification does not occur Therefore, one has at the epiphyseal end of the diaphysis a dense zone of provisional calcification underneath which there are irregular masses of calcified cartilage in fibrous tissue poor in collagen Until growth ceases entirely these areas are pushed shaftward and pile up in irregular fashion in an area of the shaft which should have been ossified Still further shaftward is loose connective tissue This is a zone of rarefaction The whole irregular mass is the scorbutic lattice Though ossification is slowed down by the abnormality of the matrix resorption of bone continues and the shaft and ossified center of the epiphysis becomes thin and porous

The periosteum is abnormal also Growth continues but in an abnormal fashion *Lack of sticky intercellular matrix allows the periosteum to separate from the bone* At the zone of rarefaction in the shaft minute fractures occur and hemorrhage arising at these fracture sites spreads up and

These are the amounts necessary to maintain high vitamin C levels—tissue and plasma levels of *0.8 to 1 mg* per cent without excessive loss in the urine. Work in the United States of America and in other countries *indicates that* as little as 18 to 25 mg daily will prevent scurvy and keep the tissues half saturated, and 40 mg daily will prevent serious tissue depletion *from a* saturation level.[25–8] The League of Nations Technical Commission on Nutrition (1938) and the Vitamin C Subcommittee of the British Medical Research Council (1948) recommended 30 mg daily.[9] Ten mg daily is sufficient, in fact, to prevent scurvy for one year and maintain good healing properties of tissues even though the plasma ascorbic acid levels are 0 and the buffy coat levels almost 0. These data do not suggest that optimal nutrition is maintained by these low levels of intake. They merely indicate that during periods of deprivation, disease may be prevented by much lower levels than those usually considered optimal. On the other hand, *it is questionable whether health is greatly improved by* an intake of 80 mg rather than 40 mg, though there is some evidence from investigations on animals that reproduction is improved and that other vital functions are more efficient.[30]

An intake of 100 mg daily produces the maximal level of ascorbic acid in the plasma of fasting persons (1.12 mg) and minimal loss in the urine (20 mg).[31] Eighty to 100 mg of ascorbic acid daily will saturate the tissues (buffy coat levels of 24.2 mg per cent), and maintain a high serum level (0.8 mg per cent).[3]

Many factors increase requirements for ascorbic acid. Recovery from scurvy seems to do this at least temporarily. Pregnancy, lactation and thyrotoxicosis increase the amount of the vitamin required each day. Diarrhea increases fecal losses, and achlorhydria decreases the amount of the vitamin absorbed before it is changed chemically to inactive substances.

Other factors tend to decrease plasma levels. Chronic inflammatory diseases and acute and chronic infection sidetrack the vitamin from the plasma to storage depots in the tissues. Surgical operations and burns have the same effect but to an even greater degree. Cold atmosphere increases the urinary excretion of ascorbic acid and dehydroascorbic acid, but administration of the vitamin does not hasten adaptation to cold.[3] In general the same circumstances that increase the need for other vitamins, or sidetrack them from the plasma, have a similar effect on ascorbic acid.

Pathology and Pathologic Physiology.—The pathologic effects of ascorbic acid deficiency are most apparent in structures of mesenchymal origin: newly formed fibrous tissue, teeth, growing bones and blood vessels.[11,33,34] These changes are the ones which account for the gross abnormalities which appear when human beings, other primates, and guinea pigs are deprived of dietary ascorbic acid. Other animals synthesize the vitamin and therefore are not dependent on exogenous sources. They accomplish the conversion of glucose to ascorbic acid by the following reactions: D-glucuronate $\overset{TPNH}{\rightleftarrows}$ L-gulonate $\overset{DPN}{\rightleftarrows}$ (3 keto L-gulonate)→ L-ascorbate. Human beings lack the enzyme system necessary for the conversion of 3 keto-L-gulonate to L-ascorbate.[34a]

exists in this country One may still find it on the pediatric and medical wards of large municipal hospitals In the infant between four and twelve months it occurs because the processed milk formulæ fed from birth are deficient in ascorbic acid unless the manufacturer has fortified them with this vitamin If the infant s chief food is unfortified and if he has refused the citrus fruit juice advised by the pediatrician scurvy is usually the result In later life, scurvy is limited almost entirely to bachelors, food faddists or chronically ill individuals who have lived for many months on diets devoid of fruit juices or vegetables prepared so as to preserve the vitamin C content

The seasonal incidence is the same as for most deficiency diseases namely, spring and fall

The first symptoms reported in experimentally induced scurvy and by patients with the natural disease are weakness easy fatigue and listlessness Shortness of breath and aching in the bones joints and muscles follow quickly The skin usually becomes dry rough and a dingy brown color These manifestations appeared in subjects with experimentally induced scurvy after ninety days of depletion and when the buffy coat ascorbic acid level had reached 4 mg per cent [33] The first distinctive physical sign is the perifollicular hyperkeratotic papule which occurs on the legs and buttocks and later on the arms and back The hairs become fragmented, coiled and buried in the lesion These signs appeared after about one hundred and twenty days of depletion Erythema and then purpura appear around these hair follicles producing the perifollicular hemorrhage, one of the classical signs of scurvy In experimentally induced scurvy in a human subject these manifestations appeared after one hundred and sixty-five days and after the buffy coat ascorbic acid level had been less than 4 mg per cent for forty five days

Purpura appears on the lower extremities first It spreads upward and involves the skin around joints Petechiæ appear along scratch marks and anywhere there has been slight trauma These petechial spots coalesce into areas of purpura and finally if they become large enough may be called ecchymoses Sometimes an entire extremity is involved with extravasated blood Hemorrhages occur also deep in the muscle leading to brawny areas of induration and ultimately phlebothromboses

Hemorrhages occur also into joints causing hemarthroses manifested by local heat swelling pain and immobility Ultimately the skin overlying the joint becomes discolored from the hemolyzed blood in and around it Hemorrhages of the splinter type may be found under the finger nails Here they lie side by side parallel to the long axis of the finger and form a palisade near the distal end of the nail

As the deficiency becomes more severe the gums become swollen blue red, spongy and very friable At first these lesions are merely purpuric spots at the tip of the interdental papillæ However as more bleeding occurs in the gums thromboses occur in the vessels and infarcts result in the blue red color The swelling may become great enough to cover the teeth and obscure them from view As has been mentioned before the ultimate result is gangrene and separation of the devitalized tissue at the gingival margin This process occurs only in subjects with teeth imbedded

down the shaft under the periosteum, stripping this layer back as far the epiphysis but not beyond Thus, the subperiosteal hemorrhage occu

A similar pathologic process effects the teeth Abnormal matrix se arates the pulp from the dentine and the dentine becomes porous A sorption of alveolar bone occurs, but abnormal matrix precludes recalcific tion The teeth become loose and fall out or may be easily pulled out the patient himself

Apparently, similar changes take place in capillary walls Intercellul cement substance, equivalent to bone matrix or ground substance defective and the vessel walls become fragile and porous This increase fragility and permeability results in petechiæ, ecchymoses, hematomas, ar a positive "tourniquet" or Rumpel-Leede test When such hemorrhag occur in the gums, which are supplied by "end capillaries" which cann form anastomoses freely with adjacent capillary beds, blood supply is c off and infarcts form in the interdental papillæ The gums become swolle blue red, boggy and friable They bleed readily when touched Infectio so common around the poorly-kept teeth of chronically malnourished pe sons, spreads rapidly, increasing the foulness of the mouth The end sta is gangrene of the gums Petechial hemorrhages occur in the viscera b usually there is no gross bleeding, though the guaiac test for occult bloo will usually be positive in the stool and erythrocytes will be found in th cerebrospinal fluid Occasionally gross cerebral and visceral bleedin occurs

There has been a suspicion for some time that ascorbic acid might b involved in adrenocortical function, since administration of ACTH de pletes the adrenal gland of its very large ascorbic acid stores Howeve there is no evidence either in guinea pigs, or human beings that ascorb acid is involved in the formation of any of the oxysteroids, or that adrena function is impaired in scurvy [38–44] In fact, stress attendant upon the de velopment of scurvy increases by 10 times the 17-hydroxycorticosteroid in the blood of guinea pigs [45]

Exactly how the biochemical abnormalities found in ascorbic acid de ficient organisms cause these pathologic developments in animals an human beings with scurvy is not known At the present time, students o the subject cannot link changes in oxidation reduction potential or in th metabolism of tyrosine and phenylalanine with such pathologic result as deficiency of intercellular matrix and ground substance There i evidence, however that ascorbic acid facilitates the conversion of a collage precursor containing proline to collagen containing hydroxyproline [45a]

The pigmentation of the scorbutic patient might be due to a defect i dihydroxyphenylalanine (dopa) metabolism and the occasional instanc of megaloblastic anemia found in the scorbutic subject might be due to a abnormality in the conversion of folic acid to folinic acid The forme relationship is purely hypothetical, the latter has been questioned b competent investigators It is obvious that there are still very wide gap in our knowledge concerning ascorbic acid metabolism and the pathologic physiology of ascorbic acid deficiency

Clinical Scurvy —Scurvy is a rare disease in the United States of America, though it is probable that much subclinical ascorbic acid deficiency

exists in this country One may still find it on the pediatric and medical wards of large municipal hospitals In the infant between four and twelve months it occurs because the processed milk formulæ fed from birth are deficient in ascorbic acid, unless the manufacturer has fortified them with this vitamin If the infant's chief food is unfortified and if he has refused the citrus fruit juice advised by the pediatrician scurvy is usually the result In later life scurvy is limited almost entirely to bachelors, food faddists or chronically ill individuals who have lived for many months on diets devoid of fruit juices or vegetables prepared so as to preserve the vitamin C content

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tooth roots or snags. Infection in the gums predisposes to earlier appearance of these lesions. Though hemorrhages may occur elsewhere in the buccal cavity, the typical gum lesion does not spread from the gingiva.

Teeth loosen in alveolar bone and may be rocked back and forth and even extracted by the scorbutic patient. Once the tooth is out, the lesion recedes slowly but complete healing is delayed until ascorbic acid is supplied. This gum lesion occurs very late in the course of natural or experimentally induced human scurvy.[8,9]

Old ulcers and scars become red and break down. New wounds fail to heal, or when apparently healed, break open when only slight stress is exerted upon them. Tests of wound healing, tensile strength of scars and histologic appearance of biopsy material from such scars amply confirm these statements. Such defects in the healing process occur only in severe and advanced scurvy or when the level of ascorbic acid in tissues, buffy coat and plasma as well as grossly abnormal saturation tests indicate very severe depletion of ascorbic acid.[11,35–37]

Petechial hemorrhages may occur in the brain and result in transient neurologic manifestations, major convulsions or actual intracerebral hemorrhage though the last is rare. A bloody pericardial effusion may occur and a little blood may appear in urine and stool, but seldom is bleeding sufficient to cause frank anemia.

The scleræ become icteric, the skin a grayish yellow color. The temperature is elevated to 101° to 102° F. The pulse is rapid and nails and lips become cyanotic. Blood pressure falls gradually, Cheyne-Stokes respirations appear, and the patient becomes more dyspneic and confused. Convulsions coma and death may supervene.

Scurvy in Infancy and Childhood.—Infants on milk diets unsupplemented with fruits and vegetables are likely to develop scurvy. The lesions usually appear between the sixth and eighteenth month of life, though they have been reported as early as the fourth month. The disease differs from that found in the adult principally because the growing bones of the infant react differently to ascorbic acid deficiency than do mature bones. Loss of appetite and listlessness appear only a few days before the overt lesions. With the onset of clinical signs, the infant lies with legs drawn up on its abdomen. It cries when its legs or arms are touched or moved. Tender swellings appear at the ends of the long bones due to subperiosteal hemorrhages. These do not break into the joints, however. The bones most frequently affected are the femur at its lower end and the humerus at its upper end. Costo-chondral separation may occur, and, as a result, the sternum may sink inward slightly, leaving a sharp elevation on the rib side of the junction. Thus, the scorbutic rosary is formed. Purpura may appear and if the teeth have erupted, the gums may be blue red and swollen from extravasated blood. This lesion appears most often around the upper incisors. Hemorrhages may occur in the viscera and if treatment is delayed dyspnea, cyanosis, convulsions and death may follow in rapid succession.

In the infant, the earliest signs of scurvy may be discovered by roentgenograms of the bones.[46] These lesions do not, however, appear in the bones of adult persons with scurvy because bone growth has ceased. The

infantile ankle and wrist are affected first A defect or crack appears at the anterior corner of the fibula or at the outer corner of the lower end of the radius just proximal to the epiphyseal line This is known as the corner sign and is due to microscopic fractures in the zone of bone growth at the end of the shaft Epiphyseal separation may occur and is caused by the junction of several of these cracks The scorbutic white line is the most distinctive x ray sign and also is found just proximal to the epiphysis It is due to piling up of calcified cartilage in the zone of provisional calcification which has not been destroyed in the normal fashion The cortex of the bone is thinned producing a ground-glass appearance and making the white line more prominent The epiphyses look like halos because they thin out except for the heavy white line around the outer edge equivalent to the zone of provisional calcification where bone growth should be taking place The scorbutic rosary, already mentioned is also a distinctive roentgenologic manifestation

The subperiosteal hemorrhages cannot be seen in the x-ray until healing and calcification begin in the hemorrhage Then they produce distinctive x ray shadows with laminated appearance (see Chapter 17 p 507)

Laboratory Features of Vitamin C Deficiency — A person whose tissues are saturated with ascorbic acid will have a plasma ascorbic acid level of 0 8 to 0 1 mg per cent a whole blood ascorbic acid level of 1 to 1 2 mg per cent and a buffy coat ascorbic acid level of 25 to 38 mg per cent Should such a person eliminate from his diet all foods containing vitamin C his plasma ascorbic acid level will reach 0 to 0 1 mg per cent in about forty days, and by this time little ascorbic acid will be found in the urine His whole blood ascorbic acid level will reach 0 in eighty to ninety days and his buffy coat level will approximate 0 in about one hundred and twenty days The first manifestation of scurvy will not appear before the one hundred and sixtieth to one hundred and seventieth day [9 36] Therefore the plasma and urine ascorbic acid levels indicate only the amount of ascorbic acid intake for the preceding few weeks the whole blood level is a somewhat better indication of tissue saturation or unsaturation and the buffy coat level is the best index of ascorbic acid nutrition It most accurately reflects the saturation of the tissues and when it has fallen to 0 clinical scurvy is likely to be present If ascorbic acid has not just been administered, any amount beyond the limit of accuracy of the methods found in plasma whole blood or buffy coat is incompatible with a diagnosis of scurvy The dichlorophenol indophenol method is accurate to about 0 1 mg per cent

There are other tests to determine the degree of saturation of the tissues with ascorbic acid and at times these may be found useful in supporting a clinical diagnosis of scurvy There are several procedures that have been reasonably standardized

(1) Measurement of the twenty-four-hour urinary excretion of ascorbic acid after the oral administration of a standard test dose (5 mg per pound of body weight) [47]

(2) The measurement of the plasma and urine ascorbic acid levels each hour for five hours (with the patient fasting) after administration of a standard oral dose (15 mg /kg of body weight) In severely depleted or scorbutic patients, the plasma level rises to about 0 4 mg per cent and falls

rapidly back to 0 The urine shows little if any ascorbic acid [37,48] A similar test has been worked out on the basis of ascorbic acid given intravenously [49]

(3) The administration of 100 mg of ascorbic acid by intravenous injection after which urinary excretion is determined over a period of three hours A normal well-saturated person will excrete 50 per cent of the test dose, a depleted person will excrete 15 per cent or less, and a scorbutic person will excrete less than 5 per cent [21]

Another method of determining the degree of unsaturation of the tissues of adult patients is as follows administer orally 500 mg of ascorbic acid daily in divided doses to the patient and, each morning, before the first dose, collect a sample of plasma for the determination of the ascorbic acid level A person with clinical scurvy will not have any ascorbic acid in the plasma until approximately 2000 mg of ascorbic acid have been given The plasma levels will not reach 0 8 to 1 mg per cent until 3500 to 4000 mg have been given If these values are attained more rapidly, one may assume that the tissues were not unsaturated and the patient did not have scurvy

Dichlorophenol-indophenol has been injected intradermally (0 01 cc of a solution prepared by dissolving 2 mg in 4 9 cc of water), and the rate of disappearance of the color has been used to estimate tissue vitamin C There are too many reducing agents other than vitamin C in the skin to allow for any accuracy in diagnosis of ascorbic acid deficiency [50,51]

Tyrosyl derivatives, homogentisic acid, p-hydroxyphenylpyruvic acid, and p-hydroxyphenyllactic acid are excreted by scorbutic guinea pigs when the animals are fed tyrosine A similar phenomenon has been observed in premature infants[5] and adult human beings[53] with scurvy In order to evoke this metabolic abnormality, infants are fed 1 to 5 gm and adults 15 to 20 gm of tyrosine daily and twenty-four-hour urine collections are analyzed for these compounds by the method of Medes,[54] and for reducing substances by the reduction of phosphomolybdic acid After the administration of vitamin C to scorbutic infants or adults, the excretion of these substances is greatly reduced Twenty-five mg ascorbic acid daily is sufficient to prevent the appearance of these abnormal metabolites in the urine [55]

Folic acid-deficient guinea pigs and persons with pernicious anemia excrete similar metabolic products, which disappear when folic acid is administered Folic acid also reduces the excretion of these substances in scorbutic guinea pigs, but apparently massive amounts of folic acid must be given before this metabolic defect is corrected in scorbutic infants [56,57]

In infants, alkaline phosphatase tends to be low,[58] but this is not the case in adults though they may develop osteoporosis Otherwise, lack of ascorbic acid does not cause any other specific chemical or electrolyte derangements

Deficiency of ascorbic acid does increase capillary fragility The Rumpel-Leede test[59] is a time honored method of demonstrating this abnormality It usually induces an abnormal response in the scorbutic person as it does in anyone who, for any reason, has increased capillary fragility It is performed by allowing a blood pressure cuff, inflated to a pressure midway between systolic and diastolic pressures, to remain in place on the upper

arm for fifteen minutes Some investigators prefer to standardize the test on a five-minute inflation time Three minutes after the pressure has been released, the number of petechiae are counted which have appeared in a circle $2\frac{1}{2}$ cm in diameter drawn just below the anticubital fossa Usually more than 20 petechiae are considered to be clearly abnormal and indicative of a capillary defect[60] A test making use of negative rather than positive pressure has been described[61]

Anemia does not occur in pure ascorbic acid deficiency of mild degree, such as has been observed in human subjects who have undergone five months or more of a diet deficient in vitamin C but adequate in all other essential nutrients[29,36] Even blood donations of 6000 cc or more during the period is insufficient stress to induce anemia However, most infants and adults with scurvy of spontaneous origin do have anemia It is the result of many factors whose interplay, together with the deficiency of ascorbic acid, causes blood formation to lag behind the demands for erythrocytes

In the infant on an unsupplemented milk diet deficient in iron, the anemia may be microcytic and hypochromic and the bone marrow normoblastic, since iron deficiency, as a limiting factor, usually takes precedence over other deficiencies[6,63] At other times it may be macrocytic or normocytic and the bone marrow megaloblastic, due to the combined deficiency of ascorbic acid and folic acid Various combinations resulting in dimorphic indices may occur Zuelzer[64] recognized the relationship of dietary deficiency to the development of megaloblastic anemia of infancy, and May and his co-workers[65] were able to show that monkeys, fed a similar diet, developed megaloblastic anemia shortly after scurvy appeared Though Nichol and Welch[21] as well as other investigators have shown that ascorbic acid is necessary for the conversion of folic acid to folinic acid and there are indications that ascorbic acid may have other functions in folic acid metabolism, May[66–68] was unable to link any of these relationships to the genesis of the monkey anemia He concluded that the ascorbic acid deficiency acted as a stress factor of sufficient degree to increase the requirements for folic acid to the point that megaloblastic anemia appeared Either folic acid or ascorbic acid will induce a clinical response but vitamin B_{12} is inactive It is probable that, by analogy with the monkey anemia, megaloblastic anemia of infancy occurs because of a combined deficiency of folic and ascorbic acids One-fourth of all infants with this type of anemia are scorbutic, the anemia responds to folic acid but seldom to vitamin B_{12}, and, since most processed milk products used for infant feeding have been fortified with ascorbic acid megaloblastic anemia has almost disappeared

In the adult person with anemia of scurvy the situation is more complex[69–75] An occasional example of the megaloblastic type of anemia has been described It is probable that these cases are equivalent to megaloblastic anemia of infancy and are due to combined folic acid and ascorbic acid deficiencies The anemia, in these instances responds with reticulocytosis and erythrocytosis when vitamin C is given Most persons with scurvy do not have this type Instead they have a normocytic or slightly macrocytic normochromic type with high initial reticulocyte count, normal

leukocytes and platelets, and hyperbilirubinemia of the indirect reacting type which is out of all proportion to the amount of bleeding into the skin and viscera. The bone marrow is usually normally or slightly hypocellular, with a relative increase in normoblasts. The serum iron levels are normal or high.

It is possible that all of this picture is the result of bleeding into the tissues. On the other hand, severe anemia has been noted in scorbutic persons who have little evidence of such bleeding and, when vitamin C is administered, normoblastic hyperplasia of considerable degree has been noted in the bone marrow before the initial reticulocytosis subsides. It seems likely that ascorbic acid deficiency has a more direct effect on blood formation and on the genesis of anemia than merely by causing a bleeding diathesis.

In the adult as well as the child, chronic general malnutrition, chronic infection, chronic liver disease, and external blood loss may complicate and somewhat alter the type of anemia described above. However, there is good clinical evidence that ascorbic acid deficiency has a deleterious effect on blood formation, but whether this is a direct effect or an indirect one through interference with folic acid metabolism is unsettled. Most recent studies[76] favor the latter point of view, but it is probable that the anemia of scurvy is the result of the interaction of many etiologic factors, which vary in importance from patient to patient.

Ascorbic acid is related in some way to pernicious anemia and therefore to folic acid and vitamin B_{12} metabolism. Patients with pernicious anemia tend to have low plasma and buffy coat ascorbic acid levels,[77] even though they have been eating a diet of normal ascorbic acid content. Many such patients will respond to ascorbic acid administration with reticulocytoses and occasionally with a distinct increase in erythrocytes.[78] During World War II in England, persons with pernicious anemia on ascorbic acid-deficient diets required more liver extract to maintain a satisfactory remission.[79] The exact significance of these observations is still unknown.

Effect of Ascorbic Acid in Scurvy.—Persons with scurvy respond rapidly and dramatically to as little as 25 to 50 mg. of ascorbic acid daily. Usually the therapeutic dose is higher, in the range of 300 to 500 mg. daily. These amounts may be given orally in divided doses or parenterally as sodium ascorbate. All bleeding ceases within twenty-four hours, the patient becomes afebrile and recovers from his apathy and depression. Appetite improves and signs of mental confusion, hypotension and restlessness disappear. Gums begin to heal and are usually normal in color at the end of three or four days. Petechiæ turn brown and perifollicular hemorrhages evolve into a pigmented follicular hyperkeratosis which may persist for several weeks. It is remarkable how rapidly large extravasations of blood will disappear—a leg, ecchymotic from hip to heel will be normal in appearance within three weeks. Elevated serum bilirubin will return to normal within a few days and severe anemia due to scurvy will have been relieved completely within three to four weeks.

In the scorbutic infant, the response is even more dramatic. Pain has subsided in twenty-four to thirty-six hours, and within a few days laminated calcifications of the subperiosteal hemorrhages begin to appear in bone

roentgenograms The other x-ray signs disappear gradually as normal matrix is laid down and, therefore, calcification is possible again

Large doses of ascorbic acid have been used by many surgeons in their post-operative patients in order to facilitate the healing of surgical wounds This idea was based on the observations that stress situations like surgical operations and severe burns about the body lowered the serum ascorbic acid level[80, 81] and that ascorbic acid concentrated in the connective tissues about healing wounds[82] It was based also on the well-known clinical experience that scurvy impairs wound healing However, more recent data indicate that ascorbic acid metabolism is in a state of flux in post-operative patients, and that the serum levels do not correlate well with platelet white blood cell (buffy coat) levels[82]

	Ascorbic Acid (mg %)		
Average	*Buffy Coat*	*Whole Blood*	*Plasma*
20 Normal persons	15 2	0 73	0 69
200 Surgical patients	14 5	0 48	0 36

(*From Crandon Nikal and Landau*[82])

Levels in the anterior rectus fascia below 1 5 mg per cent indicate significant deficiency and are usually correlated with plasma levels of less than 0 2 mg per cent Plasma levels above 0 2 mg per cent in such surgical patients usually indicates adequate tissue saturation Only when the buffy coat ascorbic acid concentration falls to very low levels is there danger of wound disruption and examples of this difficulty are extremely rare From the experimental evidence available at present, it would appear that the low plasma ascorbic acid level in patients just subject to a stressful procedure like major surgery is due to redistribution of ascorbic acid within the body rather than to an actual deficiency of the vitamin A similar phenomenon occurs in iron and vitamin B-complex metabolism

Investigators have reported that ascorbic acid has specific therapeutic effects in a large variety of unrelated medical conditions such as rheumatic fever rheumatoid arthritis acute and chronic infections allergies, intoxications bleeding gums, peripheral vascular disease and acute and chronic renal disease These claims have not withstood the test of time However as a reducing agent of considerable potency, ascorbic acid is useful in controlling at least part of the cyanosis of chronic familial methemoglobinemia[83-85] and in large doses given intravenously it does seem to have a potentiating effect on concurrently administered mercurial diuretics When given by mouth in conjunction with organic food iron it may increase the amount of iron absorbed from 10 to more than 30 per cent[86]

Ascorbic acid is a substance of great physiologic importance and is probably involved in a very large number of intracellular chemical reactions When symptoms or signs are the result of a deficiency of this substance, administration of it will dramatically relieve these manifestations There is no clear evidence that saturation rather than half saturation of the body tissues with ascorbic acid will lead to significantly better health and attempts at supersaturation are not only illogical but wasteful

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BIOFLAVONOIDS

In 1936 Szent Györgyi[1] observed what he interpreted to be synergistic potentiation of the antiscorbutic effect of vitamin C by extracts of red pepper and lemon. The active materials in these extracts, later shown to be flavones or flavonols, were reported to decrease capillary bleeding and prolong life in scorbutic guinea pigs and to overcome vascular purpura of human beings due to many different causes. This group of substances

was called vitamin P to denote its effect on capillary permeability. None of these substances has been shown to have a true vitamin effect, however, so this designation was dropped in 1950 upon the recommendation of the American Society of Biological Chemists and the American Institute of Nutrition.[3] The term "Bioflavonoids" has been used instead, but the biological activity of these compounds has not yet been demonstrated, though they may have some pharmacological effect.

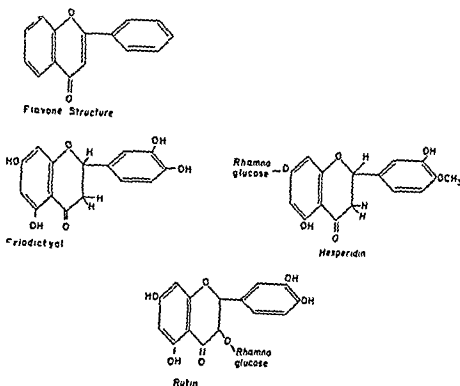


FIG 27 —Structure of the Bioflavonoids

Chemistry of the Bioflavonoids.—The basic structure of a flavone is given in Figure 27, as well as some of its substitution and reduction products in common use. These compounds can combine with sugars to form glycosides and with metals to form chelates. Quinones with reducing properties can be formed from them also. Pharmacologic effects may be dependent upon such reactions or on direct vasoconstrictor effects.

Biological and Clinical Investigations.—Though a tremendous amount of work has been done with these compounds, no deficiency state has been induced in animals nor discovered in man, and there is no proof of clinical usefulness at this time. Claims and counter claims have been made, but unfortunately there are few well controlled studies and these, for the most part, have given negative results. In the case of some of the compounds in common use, it is doubtful that a significant amount is absorbed from the G.I. tract.

There is no proof that vascular purpura, retinal hemorrhages and cerebrovascular accidents associated with hypertension have been influenced by the administration of the bioflavonoids,[4] though there have been many

reports of such benefit[5] Similar claims have been made for the purpura and retinopathy of diabetic patients[6] also without confirmation There is no proof that the flavonoids, with or without vitamin C have any beneficial effect in rheumatic fever, rheumatoid arthritis habitual abortion radiation injury, or most recently the common cold As with all such unsupported claims, a flurry of therapeutic activity is stirred up which lasts for approximately a year, and then through disappointment or because well controlled double blind studies demonstrate no effect[7,8] physicians turn their attention to other possible therapeutic tools A recent monograph the Flavonoids in Biology and Medicine presents the pros and cons of the problem[9]

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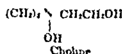
CHOLINE

By

R S Goodhart and R M Kark

Choline is the basic constituent of lecithin and sphingomyelin the precursor of acetyl choline, an important methyl donor in metabolic processes and an essential nutrient for rats chicks turkeys, and other beasts Deficiency of choline produces both renal and hepatic disorders in the rat, but it has never been shown to be associated with a specific deficiency disease in man It has been used all over the world to treat cirrhosis hepatitis and fatty liver Yet there are no data in the literature which demonstrate conclusively that it has therapeutic value

Structure, Analysis, and Metabolism —Choline was first isolated from the bile by Strecker in 1862 Its chemical name is (β hydroxyethyl) trimethylammonium hydroxide and it is widely distributed in nature



Choline

The chemical methods used for estimation of choline rely on its ability to form a colored reineckate salt, soluble in acetone Micro-biological assays can also be used to measure choline by studying the growth of a mutant strain of *Neurospora crassa*

Large amounts of choline are present in most foods consumed by man—especially egg yolks (1 7 gm /100 gm), meat (600 mg /100 gm), fish (200 mg /100 gm), and cereals and cereal products (100 mg /100 gm) Most fruits and soft vegetables contain little or no choline, but quite large amounts are present in legumes

In the 1930's Best and his colleagues began to study the genesis of the fatty livers which developed in dogs made diabetic after pancreatectomy Eventually they were able to show that choline or betaine prevented the deposition of fat in rats fed diets which were high in beef fat, or cholesterol, or sucrose Later it became evident that, in rats, diets deficient in choline produced fatty livers Hemorrhagic renal lesions which were made worse by pyridoxine were also observed to develop Other abnormalities which appeared were cirrhosis, anemia, atrophy of the thymus, enlargement of the adrenal cortex, and hypertension Hamsters, pigs, and dogs also developed fatty livers when placed on choline deficient diets, but chickens and turkeys developed perosis

In 1937, Tucker and Preston showed that methionine could cure the fatty livers of rats fed diets deficient in choline This lipotropic effect was not shared by the closely allied, sulfur-containing amino acids, cysteine and homocysteine These results indicated that the action of methionine was due to the presence in the molecule of a labile methyl group which was not present in the other two amino acids Later, Du Vigneaud showed that one of the functions of the labile methyl group of methionine was to make possible the synthesis of choline by the body Out of this work arose his concept of transmethylation reactions, now known to be of considerable importance in metabolic reactions It soon became apparent that a number of substances exist which are capable of donating a methyl group to acceptor compounds Examples of such reactions are the formation of creatine and choline from methionine, and of N^1 methyl-nicotinamide from niacin

A dietary deficiency of choline can be very largely, if not completely, alleviated by providing in the diet sources of labile methyl groups such as betaine or methionine, which permits choline synthesis in the body Also, choline deficiency is made less severe if folic acid and vitamin B_{12} which are involved in the synthesis of ethanolamine and methyl groups, are included in the diet

Although labile methyl groups are made available to the body by the consumption of foods containing methionine, choline, betaine and other allied substances, present data indicate that labile methyl groups are also synthesized in the body by fragmentation of large organic molecules, such as dimethyl glycine to synthetically useful single carbon fragments The discovery of "active formaldehyde" and of a one-carbon cycle which can synthesize choline in the body casts further doubts on the concept of Sure and others that choline should be regarded as a member of the B complex vitamins

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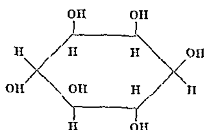
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INOSITOL

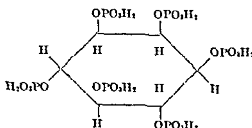
By R S GOODHART and R M KARK

Just about one hundred years ago Scherrer found that patients with diabetes, unlike healthy individuals, excreted large quantities of inositol in the urine Unfortunately, despite this significant finding and despite the fact that it is an essential nutrient for yeasts and rodents, little or nothing is known about its metabolism or biologic functions in man

Structure, Analysis, and Presence in Biologic Materials —Theoretically there are 9 possible isomers of inositol, but the only one with any biological or nutritional action is "meso-inositol" (muscle sugar or myo-inositol) which is configuratively related to d glucose



meso-Inositol



Phytic acid

It occurs widely in bacteria, yeasts, fruits, plants, and grains In the latter especially, it occurs as phytic acid, a substance which Mellanby showed many years ago could form very stable, unabsorbable calcium salts in the gastrointestinal tracts of mammals and which he believed contributed to the production of rickets in children living on marginal diets high in roughly milled grains

In 1940 Rapoport found appreciable amounts in chicken and turtle erythrocytes, however, since then, meso-inositol has been isolated from many animal tissues In 1947 Sonne and Sobotka established the range in fresh, normal, human plasma to be from 0 37 to 0 76 mg /100 ml blood Slightly higher figures were obtained from pooled plasma With regard to tissues, Woolley determined free and combined inositol in a variety of organs and dejecta of animals Large amounts were found in heart muscle (1 6 gm /100 gm) in brain (0 9 gm /100 gm), and in skeletal muscle (0 4 gm /100 gm) It is present in animal tissues largely as the phospholipid, but also as part of more complex water soluble compounds, as the free form and in an unidentified complex not readily extracted by repeated treatments with fat solvents and with water (Anderson, Halliday and Coots—1955) Analyses of inositol by gravimetric or volumetric techniques are tedious and inexact At present, most analyses are done by specific microbiological assay, using yeast growth Details can be found in Gyorgy's book on vitamin analysis

Biologic Significance and Metabolism of Inositol —While the biologic significance of inositol is almost totally unknown, its ubiquitous occurrence in nature, its synthesis in the body, and its presence in very large amounts in the heart, brain, and skeletal muscle suggest that it must have some function

In 1928 Earcott found that it was an essential growth promoting factor for yeasts Later, Woolley demonstrated that meso inositol cured alopecia in mice living on deficient diets The anti-alopecia effects of meso inositol were specific, and other isomers of inositol were not effective Later it was shown to cure dietary alopecia in rats Eagle and his coworkers found *myo*-inositol to be an essential growth factor for the *in vitro* survival and multiplication of all eighteen normal and malignant human cell lines examined by them and for one of two mouse lines

The inter-relationship with p-amino-benzoic acid was studied by Martin who showed that the addition of inositol to diets of rats precipitated a syndrome which could be prevented by feeding p amino-benzoic acid Contrariwise addition of p-amino-benzoic acid to the diets precipitated a syndrome which was prevented by feeding inositol These phenomena were thought to be related to a reciprocal action by these substances on the synthesis of vitamins by intestinal bacteria

McHenry and his colleagues believe that inositol acts like lipocaic since it prevented development of fatty liver caused by feeding biotin or beef liver extract to rats This has been denied by a number of workers, including Best Anderson Coots and Halliday have failed to confirm the claim by De Felice that inositol prevented the neuromuscular symptoms of scurvy and retarded the loss of ascorbic acid from the organs of guinea pigs on a scorbutigenic diet Not only did they fail to detect any antiscorbutic effect

of inositol, but they also confirmed the observation of Reid that the guinea pig does not require a dietary source of inositol

The consumption of inositol by man is around 1 gm /day, but only a few mg appear in the urine About 7 per cent of ingested inositol is converted to glucose, inositol is only one-third as effective as glucose in alleviating starvation ketosis After inositol feeding there is an increase in its concentration in the body, but, when rats are kept on an inositol-free diet for as long as eight months, there is no decrease in the normal total body content of inositol, which remains constant at about 14 mg /100 gm tissue Needham who did these experiments, deduced from the data that the body can synthesize inositol Halliday and Anderson have shown that the rat can synthesize sufficient inositol to meet its needs By injecting glucose-1 C^{14} and recovering *myo* inositol-C^{14} from the rat carcasses, they excluded bacterial synthesis in the intestine as a source of this inositol

Daughaday and his colleagues studied inositol excretion in diabetes mellitus in man and rats They found that in healthy men the average daily excretion was 37 mg /day with a range of from 8 to 144 mg /day This excretion of inositol was not affected by hydration or dehydration Increased output of inositol could be produced by intravenous glucose feeding and also by the consumption of 3 gm of inositol per day In healthy subjects the endogenous renal clearance of inositol was very low, but, at high plasma levels resulting from infusions, its clearance rose to levels comparable to creatinine clearance In 7 diabetic patients the average excretion was abnormally high, ranging from 280 to 850 mg /day When these patients were treated with insulin there was a sharp fall to normal levels (30 mg /day) Clearance studies with intravenous plasma loading were found to be the same in diabetics as in non-diabetics These findings indicate that inositol is filtered through the glomeruli and reabsorbed by the tubules Presumably inositol competes with glucose for reabsorption by the tubular cells In diabetes mellitus and during glycosuria resulting from intravenous infusions of glucose, the reabsorption mechanism for inositol is flooded by the tubular spate of glucose, and large amounts of inositol pass out of the body with the urine Whether this is harmful is not known Certainly these facts and its extraordinarily high content in heart muscle make it an interesting member of the B complex vitamins

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BIOTIN AND AVIDIN

By

R S GOODHART and R M KARK

Biotin—which is present in the soil, in lake bottom deposits, in bacteria, and in nearly all foods—is one of the B-complex vitamins (formerly vitamin H) While spontaneous deficiency of the vitamin is unlikely to occur in man, it is known that biotin is inactivated by a carbohydrate containing protein, avidin, which is present in egg white Thus it is theoretically possible that individuals with perverted appetites might produce biotin deficiency in themselves by the consumption of large numbers of raw eggs, and in fact this has happened

Chemistry and Metabolism —α and β biotin are fairly simple organic ring compounds Their empirical formula, $C_{11}H_{18}O_3N_2S$, and structure have been proposed by Kogl and his colleagues who crystallized small quantities from egg yolk Although no chemical or physical methods of estimating biotin are available at the present time, biological assays are done, using a number of yeast and bacterial growth techniques Other organisms, such as *Neurospora crassa* and *Candida guillermondia* have also been used

Biotin is one of the growth-stimulating substances of the bios complex and has the biological activity previously ascribed to vitamin H (the egg white injury factor) When rats consume diets containing large amounts of uncooked egg white, they develop a syndrome known as egg white injury This is characterized by an eczema like dermatitis spasticity or paralysis of the hind legs, and the development of the so called "spectacle eye" due to circumocular loss of hair The lesions produced by the diet are not due to a direct toxic action of raw egg white, but result from consumption of the protein, avidin, in egg white, which interacts with and "neutralizes," biotin in the food as well as the biotin produced in the gut of the experimental animal by bacterial synthesis Pure avidin was just as effective as raw egg white in producing the lesions in rats or mice

Daft showed that therapy with crystalline biotin would prevent dermatitis, myocardial necrosis, and other lesions produced in rats by sulfaguanidine or sulfasuxadine Apparently these compounds interfered with intestinal bacterial growth and synthesis of biotin Oppel and others have also obtained data which indicated that biotin is synthesized by organisms in the gut of man Ham and Scott found that biotin synthesis

in the intestinal tract of the rat also was inhibited by terramycin in the diet and almost completely so by a combination of terramycin and sulfasuxadine Biotin synthesis was found to be diminished when the diet was free of riboflavin niacin and pantothenic acid When starch replaced sucrose in the diet, there was an increased synthesis of biotin in the intestinal tract A dietary source of biotin is required by germ-free rats (Luckey *et al* —1955)

Biotin deficiency has been produced by feeding chicks and turkeys a diet of sucrose and acid washed, alcohol extracted casein The animals developed dermatitis and perosis Experimental biotin deficiency has also been produced in fish, cows, pigs, dogs, monkeys, and man

Sydenstricker and his colleagues fed 4 volunteers a diet rich in egg whites and low in biotin-containing foods Within five weeks the volunteers developed a fine, non pruritic dermatitis, a greyish pallor of their skin and mucosa and depression, lassitude, somnolence, muscle pains, and hyperaesthesia Later anorexia, nausea, reticulation of the skin, anemia, hypercholesterolemia, and changes in the electrocardiograph were observed All signs and symptoms disappeared within five days of therapy with parenteral biotin

Beneficial effects from the treatment of seborrheic dermatitis of infants and Leiner s disease (a widespread form of seborrheic dermatitis in infants) with biotin have been reported both in this country and in Europe (Nisenson —1957)

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CARNITINE (VITAMIN B_T) METABOLISM

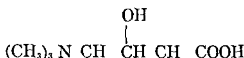
By

R S Goodhart and R M Kark

In 1947, Fraenkel while investigating folic acid in the nutrition of insects found that the meal worm (*Tenebrio molitor*) required a factor, present in the charcoal filtrate of yeast, which had not previously been

recognized.[1] To this factor he gave the name "Vitamin B_T." If the meal worms were fed on a synthetic diet deficient only in vitamin B_T, they died in four to five weeks. If this factor was added to the diet in very small amounts, they grew normally. So constant was this finding that he was able to develop a technique for bio-assay of vitamin B_T based on the rate of growth of larvae of *Tenebrio molitor*. Using this technique, he found there was a wide distribution of vitamin B_T in yeast, milk, liver, and whey, with particularly large quantities in muscle and meat extracts,[3] which since have proved to be the most potent natural sources of vitamin B_T. Although other insects, such as *Palorus ratseburgi*, could not synthesize vitamin B_T, Fraenkel and his co-workers found that most insects they studied, as well as higher animals, synthesized the vitamin in their tissues. For example, he found that hen's eggs contained little or no vitamin B_T, but substantial amounts occurred in the chicken embryo.

Fraenkel concentrated large amounts of crystalline vitamin B_T in 1948. In studies with Carter,[4] it was proved that vitamin B_T was identical with carnitine, a quaternary ammonium compound, which had been discovered in muscle, in 1905, by Gulewitsch and Krimberg.[5] Tomita, in 1927, indicated that carnitine was a gamma dimethylamine-beta hydroxy butyric acid methyl betaine, and its formula is given below.



$$(CH_3)_3N{-}CH_2{-}CH(OH){-}CH_2{-}COOH$$

Up until Fraenkel's discovery, the most intensive and valuable work on carnitine was done by Strack[6] between 1935 and 1937. In studies on muscles from cattle and dogs, he found he could not isolate or detect choline or acetyl choline either by chemical or biological methods. However, he found that the carnitine content of bovine muscle varied from between 0.02 and 0.2 per cent. Although the isolation procedure was cumbersome, he was able to obtain a pure substance, which was a quarternary ammonium compound. He then investigated its chemical properties and from biological experiments, consisting mainly of perfusion of smooth and striated muscle strips, suggested that carnitine might take the place of choline in the metabolism of muscle.

The importance of creatinine, creatine, and phosphocreatine in the metabolism of muscle is well known. In 1941, du Vigneaud[7] found that the labile methyl group of methionine was required for the synthesis of creatine from arginine and glycine. More recent work has shown that in the presence of homocysteine the labile methyl groups of choline and betaine can also be used in the synthesis of creatine from its precursor amino-acids. The similarity between betaine and carnitine is apparent in Figure 28 and indicates that one metabolic function of carnitine may be that of methyl donation. That this might be true is suggested by the fact that beta hydroxy-gamma aminobutyric acid can replace carnitine in the diet of *Tenebrio molitor*, but crotono betaine and similar compounds are not able to. Data have been presented also suggesting the possibility that carnitine in muscle in some manner serves the function of facilitating fatty-acid transfer from blood

vessels to the active sites of fatty acid oxidation within the muscle cells (Fritz and McEwen—1959)

The original efforts to study carnitine metabolism in man, and especially in patients with muscular and nutritional diseases, were hampered by methodological difficulties Fraenkel, using the bio assay technique mentioned above, had found that in mammals the carnitine content of skeletal muscle was 1 mg /g dry weight, of heart muscle, 560 mcg /g, of kidney, 412 mcg /g, and of liver 280 mcg /g Small amounts were present in the blood (7 to 14 mcg /ml), while the twenty four hour urine contained 50 to 100 mcg /ml In animal studies, the urine content of carnitine increased on a high protein diet and was reduced during starvation and by consumption of a low protein diet

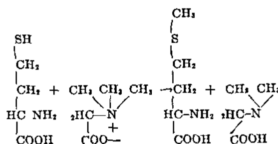


FIG 28 —Methyl donation by betaine This substance is very similar in structure to carnitine and presumably carnitine could replace betaine in the above formula to act as a methyl donor in muscle

Early in 1954, Ansel, Bhattacharyya, and Rix[8] developed a chemical method for the measurement of carnitine in small amounts of body tissue and fluids This is based on the degradation of carnitine to trimethylamine, by heat, in the presence of a strong alkali In healthy individuals, the range for serum and plasma was found to lie beteween 860 and 1330 mcg /100 ml , and the urinary excretion ranged from 80 to 130 mg /twenty-four hours Muscle obtained either through biopsy or at autopsy contained 800 to 2000 mg /g dry weight These results compare favorably with those of Fraenkel s bio assay data

Studies of healthy individuals consuming fixed diets in a metabolic unit[9] indicate that fluctuations of carnitine excretion and of blood levels in man are related to the carnitine content of the diet On diets very low in carnitine or on protein free diets (which were also very low in carnitine) the urinary excretion fell to 70 mg /twenty four hours, while it rose to 200 mg /twenty-four hours with high protein (high carnitine) diets When the protein content of the diet was reduced from 190 gm /day to 153 gm /day, the urinary excretion of carnitine fell from approximately 200 mg to 150 mg /twenty-four hours The serum carnitine levels also changed with the dietary intake of portein (and of carnitine), so that high levels were found when large amounts of carnitine were excreted in the urine, and vice versa

From the data available, there seems to be, in health, a close parallelism between creatinine and creatine excretion and carnitine excretion

Carnitine excretion and metabolism have been studied in a number of patients, ill with malnutrition, alcoholism, metabolic diseases, and muscular disorders[10] Preliminary data indicate that the decrease in carnitine excretion observed in most of these patients may be related to either poor dietary intake of protein or a decrease in muscle mass

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Chapter 12

Fluid and Electrolyte Balance

By Carl Alper

INTRODUCTION

Water and electrolytes provide essential building materials for the protoplasm of the cell, just as do proteins. Consequently, the tissue cell is in dynamic equilibrium with respect to water and electrolytes as it is with proteins. That is, the cell may be in fluid or electrolyte balance, it may be in positive balance if it is accumulating the component, or in negative balance if it is losing the component. In contrast to the nutritional balance of carbohydrates, fats, and proteins, accumulation or loss of water and electrolytes may lead to acute difficulties.

The nutritional requirement for water and electrolytes to maintain fluid and electrolyte balance is that amount which will replace the daily obligatory losses in the normal physiologic processes. From the nutritional point of view, it is quite obvious that any defect in fluid and electrolyte metabolism is not the result, usually, of deficient or excessive intake of nutrients but rather it is a result of (1) abnormal losses, (2) abnormal retention, (3) defective intestinal absorption, and/or (4) altered distribution of fluid and electrolytes. The nutritional problem then is one of the adjustment of fluid and electrolyte disequilibrium, that is, (1) to repair the composition of the body fluids qualitatively and quantitatively and (2) to restore and maintain the osmolar composition of the body fluids. Increased requirements are usually associated with abnormal losses due to metabolic imbalance, such as in vomiting, diarrhea and fever, and/or the deposition of new tissue protein since the lean mass of the body contains about 70 per cent water.

The concept of metabolic balance as related to fluid and electrolyte metabolism is not only concerned with the dynamics of intake and output of nutrient materials. It is concerned also with the shifts which may occur within the body compartments and the factors which control these internal shifts.

WATER METABOLISM

The Primary Position of Water.—Water plays a major role in cellular metabolism as well as being an important structural component of the body. Structurally, approximately 70 per cent of the lean body mass is water, giving volume and form to the soft tissues. From the metabolic point of view, water, as the principal solvent, serves as an inert vehicle for dissolved and emulsified components transporting nutriment via the circulating blood and lymph to the tissue cells and conveying secretions and

Sometimes the question arises as to whether it is correct to speak of a given body compartment, specifically or to speak of "tracer space" Another explanation for the extent of variation, especially in the values for total body water may be the factors of age and sex The sex factor may be dismissed readily because of the known differences in body fat contents in males and females The age factor has not been studied sufficiently but it is well known that the body water content falls rapidly from *the first to fourth years Then the proportion of body water falls gradually until the attainment of 'biological and chemical maturity" (E G the* early human embryo—97% H_2O, newborn 77%, adult 60%) It might be well to restudy this problem as a function of the decade of life span and sex

The Dynamics of Water Exchange —Waters enter the body as the greater part of the solution imbibed and as a preformed component of the solid foods ingested In addition, some water is formed within the body by the oxidation of hydrogen

Solid food rarely contains less than 70 per cent of preformed water, and frequently more than 80 per cent In metabolism, the amount of water produced by various food substances varies The range of vlaues found in *the literature are 0 39 to 0 41 gm water per gm of protein, 0 56 to 0 60* gm water per gram of carbohydrate, and 1 07 gm water per gm of lipid

TABLE 36 —WATER BALANCE
(Average Individual)

Water Intake	*Volume (ml)*
1 Liquid food (H_2O, coffee, milk, soup)	1100
2 Solid food (moisture)	500–900
3 Water of oxidation	400
	2000–2400
Water Output	
1 Vaporization (400 ml expired as moist air lung) 600 ml skin sweat (heat of metabolism 1 gm H_2O removes 0 58 Kcal)	920–1000
2 Feces	80–100
3 Urine	1000–1300
	2000–2400

Although fluid balance is defined as the equilibrium between water intake and water output, body fluids are dilute solutions of electrolytes, non-electrolytes, and macromolecules Table 36 illustrates the gross water balance in an average individual It is observed that water balance cannot be estimated by simply comparing fluid intake with urinary output Such a procedure ignores much of the intake and output of water The loss of water through the skin and lungs almost equals that voided in the urine In *dry hot climates this volume may be greater still* even though the individual is not visibly sweating By means of a delicate balance, if allowance is made for food ingested and urine and feces excreted, a rather steady loss of weight called *"insensible loss," may be observed*

If the normal physiologic state is to be maintained, the amount of water lost from the body daily has a certain fixed lower limit. This value is dependent upon the water evaporated through the lungs and skin, that required for external secretion such as milk, and that required for the elimination of solid waste in the feces and urine. The upper limit is flexible, depending upon the capacity of the normal kidney to concentrate urine. The normal kidney is able to secrete a urine with a specific gravity of 1.015 to 1.035. This permits the excretion of waste solids with varying amounts of water. The pathologic kidney has commonly a more limited power of concentrating the urine than a normal kidney. With marked impairment of renal function the kidney is able to provide for the elimination of waste solids only by secreting a large volume of dilute urine. On occasion, the normal kidney may excrete a large volume of urine when a metabolite in abnormally large quantity or a foreign substance with limited water solubility must be eliminated. Drugs and their metabolic products fall into the latter category. On the other hand, metabolites such as glucose and ketone bodies may accumulate in excessive amounts in diabetes mellitus.

The ultrafiltrate of the glomerulus is essentially the same as a protein-free filtrate of plasma. Consequently, the kidney must perform osmotic work to yield a urine with a specific gravity greater than 1.010. The glomeruli of the normal human kidney offer a filtering surface of approximately 1.5 square meters. Through the glomeruli filter from 150 to 200 L. of ultrafiltrate daily. As the filtrate passes down the 15 mm. of proximal convoluted tubule, the equal length of the Henle loop, and the 5 mm. of distal tubule all of it but the few liters of urine excreted every day is reabsorbed usually with elevation of the osmotic pressure of the urine to much above that of plasma. The reabsorbed fluid passes into the plasma that has lost anions, cations, and organic metabolites in passage through the glomerular capillaries before reaching the tubular circulation. The high colloid osmotic pressure of this concentrated plasma facilitates the reabsorption of water.

Of the solids in the glomerular ultrafiltrate, (Table 37) some of the *high threshold substances*, such as glucose, chloride, sodium, potassium, and

TABLE 37.—CONSERVATION OF BODY WATER AND ELECTROLYTES

Comparison of Concentration of Various Substances in Glomerular Filtrate and Urine
(Filtration Rate 130 ml./min. 180–200 L. in 24 hr.)

Substance	*Glomerular Filtrate*	*Filtered in 24 hours Assume 180 L*	*Urine*	*Significance*
Urea	0.150 g./l.	27 g.	15 g./L.	55 % reabsorbed
Sodium	142 mEq./l.	25,562 mEq.	120 mEq./l.	99.6 % reabsorbed
Chloride	103 mEq./l.	18540 mEq.	110 mEq./l.	99.4 % reabsorbed
Potassium	5 mEq./l.	900 mEq.	50 mEq./l.	93 % reabsorbed
Phosphate	1 mEq./l.	180 mM.	25 mEq./l.	83 % reabsorbed
Sulfate	1 mEq./l.	180 mEq.	20 mEq./l.	74 % reabsorbed
Glucose	100 mg./100 ml.	18000 mg.	0	100 % reabsorbed
Ammonia	0 mEq./l.	0	30 mEq./L.	Total secreted

the amino acids, are reabsorbed to such an extent as to be found in the urine either not at all or only in low concentrations When these substances are present in the plasma in higher concentration than normal, they appear in the urine in higher concentrations than usual

Other constituents of the ultrafiltrate (Table 37) are reabsorbed relatively little, these are the *low-threshold substances,* such as urea, uric acid, the phosphates, the sulfates, creatinine, and foreign substances The reabsorption of creatinine and inulin appears to be zero

Consequently, the normal adult is able to excrete from 25 to 1200 ml of urine per hour Ordinarily the output is from 1 to 2 L per day It is in inverse proportion to the water eliminated by the lungs, skin, and bowel, and in direct proportion to the water ingested

Intermediate Water Exchange —The common exchange for a 70 kg man of from 2 to 4 L per day between body and environment gives an extremely incomplete picture of the circulation of water in the body (Table 38) In addition to the circulation of the blood, there is the flow

TABLE 38 —INTERMEDIATE WATER EXCHANGE

Body Fluid	*Volume*
Saliva	500–1500 ml /24 hr
Gastric juice	1000–2500 ml /24 hr
Bile	100– 500 ml /24 hr
Pancreatic juice	700–1000 ml /24 hr
Intestinal juice	700–3000 ml /24 hr
Total gastrointestinal secretions	3000–8200 ml /24 hr
Wangensteen drainage	up to 6000 ml /24 hr
Circulating lymph	1500 ml
Circulating plasma	3500 ml
Plasma filtered through glomerulus	180–200 L /24 hr
Perspiration	50–4000 ml /24 hr
Milk	0–900 ml /24 hr

of fluid from the arterial end of the capillaries into the tissue spaces, with passage to and from the tissue cells, and return into either the venous end of the capillaries or the lymphatics Furthermore, passing from inside the body to outside the body proper are two exchanges of water of great magnitude The first is the secretions of the gastrointestinal tract (Table 38), estimated for a 70 kg man at between 7 and 10 L per day These fluids are secreted from the glands into the gastrointestinal tract, and mostly reabsorbed from points lower in the gut The second is the glomerular filtrate, estimated for a 70 kg man at perhaps 120 to 190 L per day, which is poured into the lumens of the renal nephrons and, except for a few liters excreted as urine, is reabsorbed The gastrointestinal secretions, except for saliva, have total electrolyte concentrations approximately equal to that of serum, but of different composition The glomerular filtrate has an electrolyte composition essentially the same as that of serum

Water Exchange Across Membranes —To maintain the constant composition of the various body compartments in the presence of a variable intake of nutriment and water and a variable external environment which

is offset by a variable output of fluids, it is necessary for one compartment more or less to play the role of a storage site for water and electrolytes The elastic adjustment of this compartment, the extracellular extravascular (interstitial fluid) compartment, permits the body to maintain the homeostasis of the intravascular fluid and the intracellular fluid In the process of ingestion, materials are absorbed across the intestinal barrier at rates dependent upon the nature of the substances These materials are transported by means of the intravascular fluid the volume of which is relatively stationary, from one organ tissue to another The intravascular fluid is in equilibrium with the interstitial fluid compartment which is the labile storage depot for fluid and electrolytes This compartment, which is relatively variable in size, serves to distribute or collect materials within each organ in behalf of the ultimate consumers, the tissue cells Excessive accumulations of water or electrolytes are ordinarily prevented by excretion through the kidneys The processes of glomerular filtration, tubular secretion, and tubular reabsorption are controlled by hormones and enzyme-catalyzed reactions Consequently since all the compartments are in equilibrium, any distortion resulting from pathology makes it necessary for all associated equilibria to undergo readjustments of a compensating nature Thus the over all function of this dynamic equilibrium of water and electrolytes is to minimize distortions of temperature, volume, composition, and distribution of body fluids

According to newer concepts about 5 per cent of the body water in ECF compartment has been designated transcellular water This fluid is found in the hollow organs and composition-wise is much like interstitial water Its functions are (1) to lubricate joints and other areas where organs rub or slide against one another, (2) to serve as a protective distributor of pressures for various structures, (*i e* the developing fetus, to distend the eyeball to maintain form and function) and (3) to provide an emergency source of water

The internal membranes of the body which separate fluids permit water to traverse them without restraint If fluids in a system contain a solute to which the membrane is freely permeable, it will distribute itself uniformly throughout the water of both compartments and it will have no influence on the distribution of water between the compartments The partition of water is determined by the partial osmotic pressure of those solutes to which the membrane is impermeable

The fluid exchanged between blood and the extravascular spaces contains all of the solutes except the colloids The total osmotic pressure of the serum is about equal to that of a solution containing 310 mM of undissociated solute per liter (310 mOsM) The effective difference in osmotic pressure across the capillary wall in the equilibrium between the fluids of the serum and the extravascular compartment is equal to the partial osmotic pressure of the plasma proteins Fluid equilibrium is achieved by the opposing tissue tension of the capillary

Exchange of water between cells and the surrounding aqueous medium entails changes in the concentration of all cellular constituents Of the cations, sodium is osmotically most active, since a change in sodium ion concentration provokes the concomitant movement of water

On the other hand K^+ and organic phosphate are osmotically inactive. They can vary considerably in concentration without comparable alterations in water distribution. Consequently, an equilibrium between osmotic pressure and capillary pressure and tissue tension would minimize the movement of fluid.

Distribution of Solutes.—The tissues and body fluids are iso-osmotic despite great differences in the pattern of their ionic concentration. Of the macromolecules, glycogen and nucleoproteins are found exclusively within the cell. In addition, proteins, enzymes, co-enzymes and nucleotides are found in much greater concentration within the cell than in the extracellular fluid. K^+, Mg^{++}, organic P, and creatine are found in much greater concentration within the cell, whereas Na^+, Ca^{++}, Cl^-, and HCO_3^- are found in greater concentration in the extracellular fluid. The concentration of $HPO_4^{=}$ is variable, depending on the degree of cellular activity, although it is generally found in higher concentration within the cell. Other solutes, such as glucose, urea, amino acids, and creatinine, are distributed equally across the cell membrane.

Factors Which Control Internal Water Exchange.—The body receives from the external environment a continual supply of such substances as oxygen, water, and organic and inorganic foodstuffs. From these materials the cells produce a great variety of metabolites which are distributed to other tissues or excreted. This constant physiological activity implies a continual movement of the various components of the body fluid compartments across membrane boundaries.

TABLE 39.—SPECIFIC EXCHANGES ACROSS PHYSIOLOGICAL BOUNDARIES

Boundary	*Specific Exchange*
Alveolar air—Blood Plasma	entrance of O_2, Loss of CO_2 and H_2O
Blood Plasma—Erythrocyte Fluid	exchange of O_2, CO_2, H_2O, Cl^-, HCO_3^- in both directions
	cations exchanged slowly
Blood Plasma—Interstitial and Transcellular Fluid (capillary walls)	exchange H_2O, inorganic ions, small organic molecules (glucose, amino acids, urea) in both directions
Interstitial and Transcellular Fluid—Intracellular Fluid *(cell membranes)*	gases, H_2O, small organic molecules diffuse readily
	cations and anions exchange selectively

The exchange of various constituents of the body fluids is governed by certain factors which maintain homeostasis between two body compartments across a boundary membrane. These factors are (1) concentration of osmotically active constituents, (2) colloid osmotic pressure of macromolecules, (3) hydrostatic pressure of the tissues, (4) semi-permeability of boundary membranes, (5) drainage and lymph flow, (6) tissue turgor, and (7) "active" transport. Under conditions in equilibrium these forces would neutralize one another.

The exchange between the plasma and interstitial fluid compartment is the resultant of filtration from the capillaries and tissue tension The endothelial lining of the capillaries acts as a semi permeable membrane which allows the free exchange of water and crystalloid solutes, but not proteins The osmotic pressure is greater in the plasma than in the interstitial fluid, due to the concentration of plasma proteins and the non-diffusable ions The organic solutes, urea, glucose, and creatinine, unionized and not subject to Donnan equilibrium, are distributed equally throughout the body fluids Since the plasma has the greater osmotic pressure, the tendency for the solutions of crystalloid solutes to move in the direction of the plasma is opposed by the capillary blood pressure

The exchange across the cell membrane which separates the interstitial fluid compartment from the intracellular fluid compartment is a resultant of the effect of the high concentration of intracellular protein semipermeability of the membrane with respect to inorganic ions, and pH of body fluids which affects the cations bound to weakly dissociated proteins

The discussion thus far has centered about the role of the osmotically active components which affect water exchange *i e* ionic and non ionic crystalloid solutes and proteins A second factor which plays a role in water exchange is the kidney's contribution to the elimination of waste products and conservation of water as discussed earlier

Finally, the endocrines also participate in the control of fluid and electrolyte metabolism

The excretion of water, electrolytes and certain specific non electrolytes is dependent upon the efficiency of tubular reabsorption Although the rate of glomerular filtration appears to be a function of the capillary pressure, tubular reabsorption is controlled largely by hormones of the posterior pituitary and the adrenal cortex Minor influences are exerted by the thyroid and the pancreas When thyroid activity is enhanced the over-all metabolic rate is increased, resulting in increased water and salt loss in insensible perspiration and sweat and in increased urinary water because of the larger load of waste products In the diabetic, hypoinsulinism results in glycosuria and ketonuria due to poor utilization of lipids Both substances require large amounts of water when eliminated by the kidneys

The posterior pituitary gland secretes the antidiuretic hormone which promotes the reabsorption of water in the proximal renal tubule In diabetes insipidus in which the posterior pituitary is non functional, up to 40 liters of urine may be voided in twenty-four hours Administration of the hormone or endocrine gland extracts causes a return to normal Normally, the antidiuretic hormone acts to reduce urine volume whenever there is an increased concentration of electrolytes in the extracellular fluids or a decreased amount of total body water

The reabsorption of sodium salts in the renal tubules is controlled by aldosterone of the adrenal cortex The diminished ability to reabsorb Na^+ by patients afflicted with Addison's disease may be corrected by the administration of active cortical extracts or aldosterone The anterior pituitary serves to regulate Na^+ absorption in that it secretes the adrenocorticotrophic hormone which stimulates adrenal cortical function

Due to the necessity of maintaining osmotic equilibrium, it appears that

both the antidiuretic hormone and the adrenal cortical steroids may have dual roles However, rather than discussing the vast amount of evidence, let us consider that the reabsorption of water requires reabsorption of salt, and that the reabsorption of salt requires reabsorption of water

Pure Water Depletion —Pure water depletion results when water intake stops completely or partially without a parallel loss of electrolytes Though water intake has been restricted, obligatory losses of water through skin, lungs and kidneys continue Consequently, the electrolyte concentration increases as the extracellular fluid volume decreases With slightly prolonged periods of dehydration the extracellular fluid compartment becomes hypertonic Water will exchange across the cell membrane in an effort to reestablish isotonicity by reestablishing the osmolar equilibrium between the compartments Thus the dehydration occurs at the expense of the cells The earliest clinical sign of water deprivation is thirst, which is observed when as little water as 2 per cent of the body weight is lost

When water depletion is mild the kidneys make an effort to compensate by excretion of a quantity of electrolytes equivalent to the water loss When water depletion is severe, the antidiuretic hormone stimulates the kidney to reabsorb more electrolytes in order to conserve body water When this occurs oliguria results

Pure Salt Depletion —Pure salt depletion occurs as a result of the abnormal loss of body fluids with the replacement of water only Clinically, this problem is observed most frequently in two specific instances The first is the laborer who perspires excessively, and drinks large quantities of water He fails to replace the NaCl in the perspiration The second is the acutely ill patient who experiences vomiting or diarrhea, or has a fistula with extensive fluid losses, or gastric or intestinal suctions with loss of large volumes of secretions If replacement therapy consists of dextrose in water with no salts, the patient becomes subject to salt depletion Unfortunately, there is no early clinical sign such as thirst to act as an alarm to announce developing salt deficiency With the replacement of the water losses there is consequently a decrease in the electrolyte concentration of the extracellular fluid As hypotonicity of the extracellular fluid develops, water will exchange across the cell membrane to re-establish isotonicity of the fluid compartments At the time when the tissue cells start to imbibe water, the kidney will excrete a low specific gravity urine, conserving electrolytes but losing water As the osmolarity of the extracellular fluid is restored the fluid volumes and tonicity of the fluid compartments will return to the normal levels Only extreme hypotonicity of the extracellular fluid compartment will lead to water intoxication

ELECTROLYTE METABOLISM

Electrolyte Composition of Body Compartments —In each compartment of major body fluids the concentration of anions and cations is equal and the electrolyte composition is maintained fairly constant These factors aid in the preservation of acid base equilibrium and of osmotic equilibrium, respectively The chemical patterns of the extracellular intravascular compartment (blood plasma) and the extracellular extravascular compart-

ment (interstitial fluid) are almost identical The only item of significant difference is the absence of, or very low protein concentration in the interstitial fluid compartment The pattern of electrolytes in the intracellular compartment differs widely from that of the extracellular compartment Inside the cell the major cation is K^+ rather than Na^+ and Mg^{++} is also present in high concentration The major anion in the intracellular compartment is $HPO_4^{=}$ rather than Cl^- The concentration of protein in this compartment is about 3 times that of the vascular compartment

Expression of Concentration in Body Fluid Problems —The units used to express the concentration of electrolytes and non-electrolytes in body fluid problems are milliequivalents (mEq) and milliosmoles (mOsM) (Table 40) The use of weight relations (mg per cent or volumes per cent)

TABLE 40 —COMPARISON OF UNITS USED IN THE EXPRESSION OF THE COMPOSITION OF BODY FLUID COMPONENTS

	Human Serum			
	mg/100 ml	*mEq/L serum*	*mEq/L H_2O*	*mOsM/L H_2O*
Cations				
Na^+	326.0	142	154	154
K^+	20.0	5	5	5
Ca^{++}	10.0	5	5	2
Mg^{++}	2.4	2	2	1
Total cations	358.4	154	166	162
Anions				
HCO_3^-	60.5[1]	27	29	29
Cl^-	365.7	103	112	112
$HPO_4^=$	3.4	2	2	2
HSO_4^-	1.6	1	1	1
Organic acids	17.5	5	5	5
Proteins	6500.0	16	17	2
Total anions	6948.7	154	166	151
Total osmotically active particles				313

[1] Volumes per cent (ml CO_2/100 ml)

does not give any indication of the physiochemical capacity of the substances For example 10 mEq (230 mg) of Na^+ are equivalent chemically to 10 mEq (350 mg) of Cl^- but 10 mg of each are not equivalent on the basis of their chemical activity By the same token 10 mOsM of Na^+ will have the same osmotic effect as 10 mOsM of Cl^-, but again 10 mg of each are not osmotically equivalent Thus it becomes necessary to express the concentrations in terms of physiochemical capacity rather than quantity for a valid interpretation of anion-cation and osmotic equilibrium

The expression of compositional values as absolute numbers without an indication of the range of values observed, would ignore the fact that any biological system is not only different from subject to subject but often differs within the same subject at different time intervals Table 41 gives some mean values obtained by Wooton and King (1953) for the major electrolytes of human serum

TABLE 41 —RANGE OF NORMAL VALUES FOR THE MAJOR ELECTROLYTES OF HUMAN SERUM*

(Summarized from Wooton and King Lancet, *1*, 470, 1953)

	Lower 1% mEq /L	*Lower 10% mEq /L*	*Upper 10% mEq /L*	*Upper 1% mEq /L*
Na^+	133	137	148	152
K^+	3 5	3 9	5 0	5 6
Ca^{++}	4 5	4 8	5 4	5 7
Cl^-	99	101	106	108
HCO_3^-	24	25	29	31

*Based on 50–100 analyses

ACID-BASE BALANCE

Metabolic Production of Anions and Cations —The normal metabolic processes result in the continuous production of acids If the ketogenic antiketogenic ratio is unbalanced, the body is loaded with organic acids due to incomplete fatty acid oxidation In addition, some fruits and vegetables provide organic acids, the metabolic destinies of which are not well known These acids include tartaric acid citric acid, oxalic acid, precursors for hippuric acid and others Furthermore, the inorganic components of food greatly influence the normal fluctuation of fixed acid and base production The fixed acid-forming elements are chlorine, sulfur and phosphorus The so-called base forming elements are sodium, potassium, calcium, and magnesium Thus the acidic or basic nature of foodstuff ash presents the extra cellular fluids with an extra burden in acid-base control (*See* Table 42)

TABLE 42 —WATER AND ELECTROLYTES AS METABOLITES

Metabolite	*Origin*	*Amount produced or utilized on a normal diet*
Water	1 Dietary	variable
	2 Metabolic Water of oxidation	about 400 ml /day
Electrolytes		
(a) Sodium	Dietary	variable
(b) Potassium	Dietary	variable
(c) Calcium	Dietary	variable
(d) Magnesium	Dietary	variable
(e) Chloride	Dietary	variable
Carbon Dioxide	Metabolic carbohydrate lipid protein	10–20 Moles/day
H_2SO_4	Metabolic protein	50–100 millimoles/day
H_3PO_4	Metabolic protein, lipid	
Organic Acids (citric acid uric acid hippuric acid lactic acid formic acid, oxalic acid beta hydroxy-butyric acid)	Metabolic carbohydrate lipid protein	

Mechanisms for the Removal of Excess Anions and Cations.—The hydrogen ion concentration of extracellular fluids is maintained at approximately pH 7.4. To achieve such constancy of acid base balance, the organism must provide mechanisms for the removal of excesses of either anions or cations.

The simplest mechanism available to provide such protection is *dilution*. When an excessive amount of CO is produced in tissue cells the concentration of HCO_3^- distributed throughout the whole of the body fluids is elevated only to a small degree, since the total body water is 70 per cent of the lean body mass.

The second mechanism which comes into play is the ability of the body fluids *to buffer excesses of anions and cations*. This is particularly important since the acids must be transported from the site of formation (cells) to the locus of excretion (lungs and kidneys), with little change in pH of the extracellular fluids. The buffer *systems* which operate both in the plasma and in the red cells are HCO_3^-/H_2CO_3, $HPO_4^{=}/H_2PO_4^-$ and organic acid buffers. In addition the plasma has the plasma proteins, and the red cells have the hemoglobin buffers.

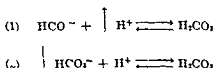
Finally the third mechanism which functions is the *excretion* of CO_2 by the lungs and the *excretion* of excess cations and anions by the kidneys along with *ammonia formation* and *hydrogen ion exchange*. Organic acids are present as the free acid rather than as the ionized salt.

Abnormalities in Acid base Balance.—The result of the mechanisms for the removal of excess anions and cations is to maintain the blood pH near 7.4 (7.35 to 7.45). Although the effect of acid base imbalance on intracellular fluids is imperfectly known variation beyond the normal range results in death. Consequently it is imperative to evaluate the degree of acid base imbalance, if any.

The evaluation of disturbances of acid-base balance depends upon the accurate measurement of one of the blood buffer systems. The pH of a buffer system is dependent upon the dissociation constant of the buffer acid and the ratio of the concentrations of the buffer salt to buffer acid.

Disturbances in acid base balance arise when an increased load of acidic or basic metabolites cannot be accommodated by the normal excretory processes. The metabolite excess may develop when the rate of production or intake of a metabolite is enhanced as in the production of keto acids in uncontrolled diabetes. It may also develop as the result of a disproportionate loss of water and certain specific electrolytes, such as occurs in vomiting and diarrhea. Another causative factor is the impairment of excretory function (renal or respiratory) with the resulting deficient or excessive elimination of substances in the presence of a normal or increased load.

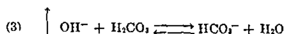
Metabolic acidosis is the result of either excessive accumulation of acids (eq 1) or the disproportionate loss of alkali (eq 2).



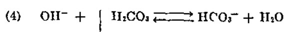
As acid is produced plasma bicarbonate is converted to carbonic acid with a resultant primary HCO_3^- deficit and secondary H_2CO_3 increase As the concentration of H_2CO_3 increases, the respiratory center is stimulated and hyperventilation ensues with the expulsion of CO When renal compensation occurs in this metabolic defect, there is a conservation of base manifested by increased reabsorption of HCO_3^- and the exchange of H^+ and NH_4^+ for Na^+, which is reabsorbed

In metabolic acidosis resulting from alkali deficit, bicarbonate ions are lost, with a resultant increased dissociation of the weak acid, H_2CO_3, and a secondary increase in free hydrogen ion In this instance renal compensation is of primary importance, whereas respiratory compensation plays a relatively minor role

Metabolic alkalosis is the result of either excessive accumulation of base eq 3) or the disproportionate loss of acid (eq 4)



$$(3)\quad \uparrow\ OH^- + H_2CO_3 \rightleftharpoons HCO_3^- + H_2O$$



$$(4)\quad OH^- + \downarrow\ H_2CO_3 \rightleftharpoons HCO_3^- + H_2O$$

As base is accumulated, plasma carbonic acid is converted to bicarbonate, with a resulting primary HCO_3^- excess and a secondary H_2CO_3 decrease As the concentration of H_2CO_3 decreases, the respiratory center is depressed, with resultant hypoventilation and accumulation of H_2CO_3 Renal compensation is effected by an increased loss of base This is achieved by a decrease in the $H^+ - Na^+$ exchange and a diminished resorption of HCO_3^-

In metabolic alkalosis resulting from an acid deficit, carbonic acid is lost, with a resultant increased hydrolysis of bicarbonate ion and a secondary increase in hydroxyl ion In this instance respiratory compensation is much less effective than renal compensation

The degree of completeness of compensation in the metabolic aspects of acid-base imbalance is questionable Such cases generally need active therapy

Acid-base imbalance resulting from respiratory disorders is due to the stimulation or depression of the respiratory center, pulmonary lesions, and mechanical obstruction of the air passages Respiratory acidosis results from a primary CO_2 excess, whereas respiratory alkalosis results from a primary CO_2 deficit Compensation in instances of respiratory acid base imbalance depends entirely upon the kidneys and may be complete

Recently Weisberg posed certain questions which might assist the clinician in the evaluation of the history and clinical course in an instance of acid base imbalance Interestingly enough, the questions are based almost entirely on the nutritional habits of the patient

(a) Has there been a normal intake of water?
(b) Has food intake been normal?
(c) Have there been any voluntary or medical restriction or additions of food or dietary intake?
(d) Has there been any weight loss?

(*e*) Has there been a loss of body secretions?
(*f*) What has been the duration and extent of this loss?
(*g*) Did the patient continue to take any fluids and/or food during this period of time?

Metabolism of Sodium and Potassium.—Both of these electrolytes are provided in the diet. Sodium is absorbed and enters essentially into the extracellular fluid compartment. It may also be transferred into the cells and become incorporated into the bone minerals. The osmotic pressure of extracellular fluid is primarily dependent upon sodium. A deficit in sodium, produced primarily from fluid losses from the alimentary tract or urinary hypervolemia, will result in a lowered osmotic pressure in the extracellular compartment with a movement of water into the cells. Increased sodium ion concentration in the extracellular fluid results in hypertonicity and *in water exchange in the opposite direction.* The crucial problem in regard to sodium balance is the ability to distinguish between alterations in the concentration of sodium and alterations in the absolute amount of sodium. For example, in water deprivation sodium ion concentration may be increased without any increase in the absolute amount of sodium.

Potassium also enters the extracellular fluid but is transferred almost entirely *into the cells. Cellular deposition of potassium is associated with* glycolysis, glycogen formation, tissue protein synthesis, and cellular hydration. Potassium leaves the cells with tissue and glycogen breakdown. These biochemical changes in the cell are associated with histological alterations in cell structure. The evaluation of intracellular potassium would be impossible in the living organism except by indirect means. Consequently, extracellular potassium serves as the index of potassium levels. Unfortunately, deficits in body potassium may exist although serum potassium levels may be elevated, even to the fatal level.

Potassium losses most commonly occur from the alimentary tract. However, diminished intake of potassium may be a contributing factor to total deficiency more often than in the case of sodium. Also renal conservation of body potassium is *less efficient than the renal mechanism for sodium* conservation. Deficits may be evaluated by the determination of total exchangeable electrolyte and electrolyte balance.

Potassium and sodium excesses are usually the result of acute overdosage by infusion.

Fluid and Electrolyte Therapy.—The objects of fluid and electrolyte therapy are (1) to supply the daily needs of the patient (including current losses via urine, skin and lungs), (2) to replace the deficit from abnormal losses as assessed from a history and with the aid of the laboratory, and (3) to replace current abnormal losses, if there are any.

The management of the majority of patients is not difficult despite the element of clinical guesswork. The most easily manageable patients are those in whom the circulating blood volume and renal function have been restored to "normal." The major problem in the clinical care of the patient receiving fluid and electrolyte therapy is to avoid gross distortion of the composition of the body fluids. Usually this is avoided if the solutions can be administered orally or rectally. If, on the other hand, therapy must

be maintained by parenteral administration, the patient should be watched closely by the physician. Laboratory assessment of the patient must be carried out according to each individual circumstance. If frequent reappraisal of the patient's status is necessary, it is suggested that serial determinations of total cations, bicarbonate, and chloride be carried out at the bedside according to the method of Scribner *et al* (J A M A, *155*, 639, 654 (1954) along with serial E C G determinations.

The restriction of sodium intake by the ambulatory patient is not difficult. The omission of salt intake at the table and from cooking alone with the use of salt-free bread will reduce salt intake to one gram per day. If further limitation is required it may be achieved by the therapeutic use of ion exchange resins.

Fluid and electrolyte therapy in surgical cases is discussed in Chapter 32.

THE ASSESSMENT OF CHANGES IN BODY FLUIDS

Changes in the amount of water and electrolytes in the body can be derived from (1) weighing techniques, (2) blood levels, (3) balance and retention studies, (4) dilution techniques, (5) exchangeable electrolyte, and (6) red cell and muscle biopsys. Rapid changes in body weight after corrections have been made for food intake, excreta and insensible water loss usually imply a change in total body water. Such measurements are more significant relative to abnormal retention of water than abnormal loss of water. Weight loss following injury or surgical trauma is more than likely indicative of rapid mobilization and breakdown of body fat stores and lean tissue masses. Clinical balances are available which will weigh accurately to 25–50 gm.

Dilution techniques aid in the absolute determination of the distribution volumes of tracer substances. Criteria for a satisfactory tracer substance have been discussed early in this chapter.

The determination of blood levels for the various electrolytes is generally very helpful. Wide normal ranges may be due to age and sex differences, as a result of the variable content of body fat. In addition, attention must be paid to those physiological factors which affect the volume of the circulating blood and so the blood levels of the various electrolytes. This difficulty can be overcome in part by determining total exchangeable electrolyte by means of an isotopic tracer.

Balance studies are a convenient clinical means to assess the state of fluid and electrolyte loss or retention. Such studies might point out discrepancies not noted by measurement of blood levels. Of course, the success of the study is dependent upon normal renal function. Studies can be carried out in any hospital.

Red cell and muscle biopsys are difficult to perform and are only valuable when carried out properly. Cellular concentrations of fluid and electrolytes provide direct determination of the composition of intracellular water.

SUMMARY

Water and electrolytes are essential dietary constituents for normal cellular metabolism. The extracellular fluid transports the nutritive

materials to the tissues and removes the waste products of cellular metabolism. The interstitial fluid compartment essentially maintains the chemical and physical equilibrium of the several body compartments. Excessive loss or gain in water and/or electrolytes is reflected in alterations in the distribution of the substances in body compartments and in the pH of the body fluids. Nutritional therapy, that is, the replacement of water and electrolytes to cover obligatory and abnormal losses, is mandatory when clinical and laboratory signs indicate fluid and electrolyte depletion or starvation.

Knowledge about biochemical changes in body composition that develop as a result of injury, starvation, pregnancy, and a number of pathological states such as Addison's disease, renal failure, diabetes, gastrointestinal obstructions, and respiratory disorders are being accumulated. However, little is known about the significance of these changes in physiological homeostasis to the patient.

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Chapter 13

Antimetabolites—Effect on Nutrition

By Thomas H. Jukes and Harry P. Broquist

INTRODUCTION

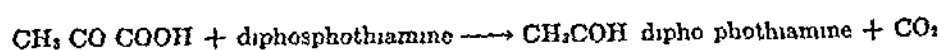
One of the broad concepts in modern biochemistry and pharmacology deals with the effect of certain specific chemicals in reversing or blocking the effects of other related substances in biological systems. The compounds responsible for these blocking effects are termed "antimetabolites" because they are concerned with preventing the utilization of normally occurring nutritional substances by living tissues.

Some familiar examples of the action of antimetabolites are the effect of antihistaminic compounds in blocking the action of histamine when it is liberated in the tissues, the inhibition of bacterial growth by the sulfonamides due to their interference with the utilization of para-aminobenzoic acid by the bacterial cell, and the increase in blood clotting time produced by Dicumarol because it blocks the normal effect of vitamin K in bringing about the production of prothrombin.

A number of comprehensive reviews have appeared on the subject of antimetabolites[1-5, 14] and two excellent books on the topic have been published.[6, 7] These works, particularly that of Martin, list hundreds of compounds which exhibit some form of antimetabolite action; in one table Woolley has compiled a bibliography on 43 metabolites and 92 structural analogs or classes of analogs which have been found antagonistic to them.

It is beyond the scope of this article to discuss more than a selected portion of this large field, and we shall confine ourselves to a brief discussion of certain antimetabolites which by their effect on animals and human beings may be of interest in clinical medicine.

Chemical reactions in living tissues are nearly always brought about by means of enzyme systems. These systems often consist of a protein component or "apoenzyme" together with one or more "coenzymes" which, in contrast to the apoenzyme, are comparatively small molecules. The coenzymes may have such functions as transferring hydrogen from one metabolite to another and are able to repeat a function many times without themselves being destroyed during the process. By this means the oxidation of many of the common foodstuffs is brought about. For example, "cocarboxylase" or diphosphothiamine is a coenzyme for the oxidation of pyruvic acid and brings about the following reaction:

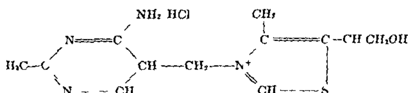


$$CH_3 \cdot CO \cdot COOH + \text{diphosphothiamine} \longrightarrow CH_3COH \cdot \text{diphosphothiamine} + CO_2$$

The CH_3COH diphosphothiamine then proceeds to oxidative reactions, and the diphosphothiamine is liberated.

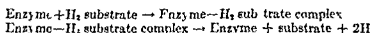
Diphosphothiamine, as its name implies contains a molecule of thiamine or vitamin B_1. Pyruvic acid fails to be oxidized in the tissues if sufficient supplies of diphosphothiamine are not present. This occurs when thiamine is deficient in the diet and this deficiency brings about such diseases as beriberi in human beings or polyneuritis in experimental animals, both of which are due to a failure of the oxidative processes which are catalyzed by diphosphothiamine.

The structural formula of thiamine hydrochloride is



Not only may the oxidation of pyruvic acid be blocked by thiamine deficiency but it may also be stopped by administering a substance termed pyrithiamine (neopyrithiamine) which has the formula shown on page 424. Pyrithiamine is an antimetabolite of thiamine, and it is thought to block the enzyme system in which thiamine normally functions. Pyrithiamine is able to do this because its molecule is so similar to that of thiamine and, to use a simple analogy, just as a key which nearly fits a lock can jam the mechanism more effectively than can a very different key, so does pyrithiamine replace thiamine in the enzyme system and block the oxidation of pyruvate.

In order to formulate a theory to explain the action of antimetabolites it is necessary to consider the nature of the action of enzymes. Metabolites which react with enzymes are termed "substrates," and the first step which is thought to take place in an enzymatic reaction is the formation of a compound between the enzyme and the substrate. This compound is known as the "enzyme substrate complex." The enzyme substrate complex then decomposes so as to yield the transformation product of the metabolite and to set the enzyme free to react once again with a fresh supply of the metabolite. This procedure is illustrated in the following diagram.

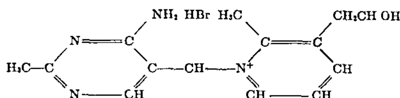


Enzyme + H_2 substrate → Enzyme—H_2 substrate complex
Enzyme—H_2 substrate complex → Enzyme + substrate + 2H

The chemical combination between the enzyme and the metabolite usually appears to be dependent upon the chemical structure of the metabolite. If we substitute a compound which is chemically quite similar to the metabolite it may combine with the enzyme to form a complex. In certain cases however this complex remains undecomposed so that the enzyme is not liberated to go through the cycle again. In this case the new compound is behaving as an antimetabolite. The enzyme has been taken out of circulation and the metabolic process is brought to a halt. This line of reasoning is used in explaining the mechanism of action of antimetabolites.

ANTIVITAMINS WHICH AFFECT THE NUTRITION OF ANIMALS AND MAN

Antithiamine Compounds.—(*a*) *Pyrithiamine* (*Neopyrithiamine*).—The production of an acute form of thiamine deficiency in mice by the administration of a chemical analog, pyrithiamine,[8] was described by Woolley and White.[9] They found that thiamine would reverse the toxic action of the analog even when pyrithiamine was administered in amounts which were lethal in the absence of added thiamine. Later chemical studies showed that the product resulting from the procedure described by Tracy and Elderfield differed from the substance which had been anticipated and the latter was prepared by a different synthesis and was named neopyrithiamine. It was assigned the following structure, and it was found to have the same biological properties as the earlier and less pure preparation except that neopyrithiamine was about four times as active as the impure "pyrithiamine."[10]



The administration of 1 mg. of neopyrithiamine per mouse was followed in seven to eight days by the appearance of typical signs of thiamine deficiency. Lower doses were also tried and 0.5 mg. of neopyrithiamine caused convulsions and death in mice which received 4 micrograms of thiamine daily on a purified diet. These reactions were not produced when the dosage of neopyrithiamine was reduced to 0.17 mg. daily, but instead there was a reduction in growth rate to about half that seen in untreated controls. It was reported by Cerecedo and coworkers[11] that, even at a molar ratio of 1 mol of neopyrithiamine to 1 mol of thiamine injected subcutaneously, the analog produced typical paralysis in mice in thirteen to fourteen days and death usually followed two to four days later.

The various hypotheses to explain the action of neopyrithiamine were described and discussed by Woolley.[12] One suggestion was that the analog interfered with the combination of diphosphothiamine (cocarboxylase) with apocarboxylase. A second hypothesis was that neopyrithiamine competed with thiamine when the latter acted as a substrate for the enzymatic synthesis of cocarboxylase, while the third possibility was that neopyrithiamine after phosphorylation competed with cocarboxylase for combination with apocarboxylase. Woolley[12] studied the synthesis of diphosphothiamine from thiamine in the blood of normal chickens and in fractions prepared from the blood. This synthesis was inhibited by neopyrithiamine, but the antimetabolite did not interfere with the combination of diphosphothiamine with yeast apocarboxylase. A competitive antagonism was found between diphosphoneopyrithiamine and diphosphothiamine for combination with the apoenzyme. The amount of neopyrithiamine required to inhibit the phosphorylation of thiamine was so large that it was

concluded that this inhibition did not explain the effect of the antivitamin on intact animals

A second analog oxythiamine in which the primary amino group of thiamine has been replaced by hydroxyl has been studied and has been found to produce effects similar to those produced by neopyrithiamine, but larger amounts of oxythiamine than of neopyrithiamine are needed to produce comparable results The effects of various antithiamine substances were reviewed at some length by Somogyi [13]

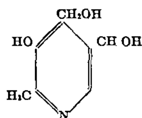
(*b*) *Thiaminase*—A disease in foxes due to the feeding of raw carp and named "Chastek' paralysis because it was first observed on the farm of J S Chastek near Glencoe, Minnesota The syndrome was described as being marked by anorexia, weakness, progressive ataxia, paraplegia and spastic paralysis with death occurring within forty-eight to seventy-two hours after the onset of neurologic symptoms [14] The pathology included degeneration of the liver and vascular lesions in the brain located principally in the paraventricular grey matter and resembling those seen in Wernicke s hemorrhagic polioencephalitis in man The disease was shown to be due to thiamine deficiency It was later shown that the carp contained a thiamine splitting enzyme Other fresh water fish and certain marine forms including clams mackerel herring and whiting were also found to contain thiaminases Properly speaking thiaminase is not an antimetabolite, since this term is best restricted to substances which do not have a destructive action upon their metabolic counterparts However, the syndrome produced by feeding raw fish containing thiaminase and its reversal by increasing the thiamine level of the diet are reminiscent of metabolite antimetabolite relationships

(*c*) "*Fern Poisoning*'—Cattle and horses are subject to a disease caused by eating bracken fern (*Pteris aquilina*) which contains a thermostable antithiamine substance or substances [15] Rats which were fed diets containing 40 per cent of dried fern lost weight and died in about twenty days The toxicity was prevented by giving 0 5 mg of thiamine daily

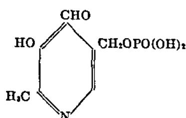
Fractionation of bracken was found by Evans and co-workers[16] to yield a thermolabile system which split thiamine into its pyrimidine and thiazole moieties The enzyme system was found to contain a thermostable dialyzable cofactor The cofactor was not identified, but thiaminase cofactor activity was found to be widely distributed in extracts of plant and animal origin such as yeast liver, urine and grass [17] Several meta-substituted aromatic primary amines were able to act as artificial cofactors as had been previously noted in other thiaminase systems [18]

Antimetabolites of Vitamin B_6—Pyridoxine, vitamin B_6, a member of the B complex, is a dietary essential for animals and its deficiency leads to a widespread and characteristic pattern of signs and symptoms Among these are slow growth seborrheic dermatitis, convulsive seizures hypochromic microcytic anemia and disturbances in the metabolism of amino acids The similarity of the dermatitis in experimental animals to acrodynia has been noted

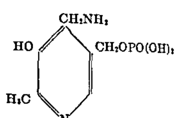
Pyridoxine is biologically active in living cells in the form of two modifications of its molecule, pyridoxal phosphate and pyridoxamine phosphate the formulas for which are as follows



Pyridoxine



Pyridoxal Phosphate

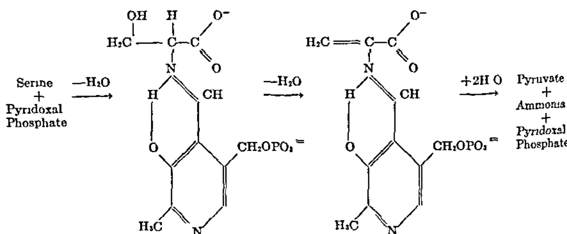


Pyridoxamine Phosphate

These substances are produced in the body when pyridoxine is fed in the diet. Pyridoxine, pyridoxal and pyridoxamine are of approximately equal biological activity when tested *with vitamin B_6-deficient rats, although* pyridoxamine shows slightly greater activity than the other two forms. In contrast, pyridoxal and pyridoxamine are much more active than pyridoxine for the growth of lactic acid bacteria.

A metabolic antagonist, 4-deoxypyridoxine, has been synthesized and has been used to bring about vitamin B_6 deficiency in human beings. This deficiency can also be produced in infants on purified diets from which pyridoxine has been omitted. The results obtained by both these methods appear to be quite similar.

It has been suggested that the aldehyde group of pyridoxal phosphate condenses with the NH_2 group of amino acids in metabolic reactions which involve vitamin B_6. This suggestion was made by Metzler and Snell[19] as a result of studies with non-enzymatic reactions involving pyridoxal. For example, the deamination of serine by the pyridoxal phosphate enzyme system would proceed as follows:



They have also postulated that the phosphate group and the nitrogen atom of pyridoxal phosphate enter into combination with the protein carrier of the enzyme. These concepts make it easy to understand why deoxypyridoxine should be a potent antimetabolite. It could replace pyridoxal in the vitamin B_6 enzyme, and the resultant product would be unable to enter into reactions with amino acids because the CHO group has been replaced by a methyl group which would not combine with an amino group.

The toxic effects of deoxypyridoxine were first described by Ott [9] who found that pyridoxine-deficient chicks were killed by doses as low as 16 micrograms of this compound, while non-deficient chicks were unharmed by doses up to 600 micrograms It was later shown that about 2 mg of the antimetabolite would neutralize the biological activity of 1 mg of pyridoxine The effect of deoxypyridoxine on the metabolism of tryptophan was studied by Porter, Clark and Silber [1] They found that the antimetabolite produced an increase in the excretion of xanthurenic acid in rats This is a sign of pyridoxine deficiency in which the metabolism of tryptophan is impaired, and xanthurenic acid appears in the urine as a consequence The excretion of kynurenine was also increased

Several investigators have used deoxypyridoxine as an anti tumor substance following leads which indicated that the growth of certain tumors is retarded in pyridoxine deficiency It was reported by Stoerck that lymphosarcoma transplants in mice failed to grow when pyridoxine deficiency was produced in the animals, and that the transplants regressed when mice were placed on deficient diets with a supplement of deoxypyridoxine An attempt to treat lymphosarcoma and acute leukemia in human patients with pyridoxine deficient diets and deoxypyridoxine was made by Gellhorn and Jones [23] Although the period of treatment was about four to fourteen days 2 patients developed toxic manifestations accompanied by convulsions which disappeared when the deoxypyridoxine was withdrawn Loss of weight and weakness were noted in all patients No regression of the diseases was noted which perhaps is not surprising in view of the shortness of the treatment period

A comprehensive study of the effects of deoxypyridoxine in human subjects was described by Vilter and coworkers [24] A total of 50 patients with a wide variety of chronic diseases received the antimetabolite for three to fifty-two weeks at a dosage rate from 50 to 500 mg daily Symptoms and signs of pyridoxine deficiency were noted in 34 of the patients lesions appeared after an average of twenty two days of treatment although in some cases only five days elapsed and in other cases no lesions developed even after a year of treatment However, the authors drew attention to the variation in batches of deoxypyridoxine Their findings indicate that pyridoxine deficiency produces symptoms which occur in deficiencies of other B vitamins, evidently there is an overlap in the symptomatology of vitamin deficiency symptoms in human beings All the signs and symptoms induced by desoxypyridoxine were relieved by administering pyridoxine pyridoxamine or pyridoxal in doses of 5 to 200 mg daily either orally or parenterally The authors noted that each of these three compounds was equally effective and there was no difference between oral or parenteral administration The low doses appeared to be as effective as the higher ones and it should be emphasized that administration of the vitamin reversed the syndrome even though dosage with deoxypyridoxine was continued This study by Vilter and coworkers is a good illustration of the production by antimetabolites of a syndrome which closely simulates the deficiency disease caused by the lack of an essential vitamin and which may be reversed by raising the level of the vitamin in the diet Furthermore, the chemical structure of the antimetabolite enables a satis-

factory explanation of the mechanism to be made, indeed, it has actually been shown that deoxypyridoxine phosphate competitively inhibits the union of pyridoxal phosphate with tyrosine apodecarboxylase[25-7] Another synthetic substance, 4-methyloxypyridoxine behaves as an antimetabolite for the chick but has a weak pyridoxine-like activity for rats and mice, indicating that these latter species can convert it to pyridoxine by demethylation

The effect of deoxypyridoxine on reproduction in rats has been studied in an interesting series of investigations by Nelson and Evans[28-31] They found that the addition of deoxypyridoxine to a diet deficient in vitamin B_6 when given to adult rats resulted in severe reproductive disturbances When the antimetabolite was added to the diet two weeks prior to breeding more than half of the female rats resorbed their litters and among the remainder the young were undersized at birth and in some cases were still born If, however, deoxypyridoxine was started three weeks before breeding, fetal death and resorption occurred in 90 to 100 per cent of the pregnant females All these disturbances were prevented by adding pyridoxine to the diet after mating had taken place, even though the animals received the antimetabolite without pyridoxine for two to three weeks prior to breeding The disturbances in reproduction were not due to diminished food consumption because rats which received the B_6-supplemented diet after breeding reproduced normally, even though the amount of food they were given was restricted to an amount equal to that which was consumed by the rats which received the antimetabolite without supplementary pyridoxine

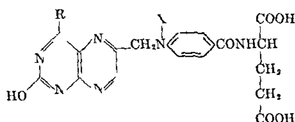
Nelson has stated that the early appearance of vaginal erythrocytes and the extreme rapidity of the resorptive process in the rats receiving deoxypyridoxine together with the early loss of the estrus cycle in the unbred rats suggested the possibility of hormonal deficiencies in these animals[30] The effects of daily injection of 1 microgram of estrone and 3 to 4 mg of progesterone were tested in the pregnant rats receiving deoxypyridoxine[33] The uninjected animals showed 90 per cent resorptions, and the injection of either of the hormones alone had no effect However, the injection of both the hormones was markedly beneficial, and pregnancy was maintained in 90 per cent of the animals, thus showing that the action of deoxypyridoxine was on the production of the estrogenic and progestational sex hormones in the mother rats The effects on the fetus are secondary to the action on the mother Nelson[30] has considered the various points at which deoxypyridoxine may inhibit the production of the sex hormones and has concluded that dysfunction of both the pituitary and the ovary occurs in animals receiving deoxypyridoxine However, the effect on the pituitary did not appear to be concerned with the production of the gonadotropic hormones, because pituitary glands from the rats receiving deoxypyridoxine contain from 5 to 8 times as much gonadotropic activity as those of normal animals[31]

Interestingly enough, the effects of deoxypyridoxine on pregnancy could be contrasted with certain other dietary deficiencies It was found that disturbances in pregnancy caused by pantothenic acid deficiency or

produced by feeding X-methyl folic acid could not be corrected by administering estrone and progesterone

A naturally-occurring antagonist of pyridoxine was found to be present in linseed meal by Kratzer and Williams[34] They found that chicks which received a diet containing 30 per cent of linseed meal grew slowly, and growth was restored when 7 mg or more of pyridoxine was added per kg of diet The growth depression by linseed meal occurred in spite of the fact that the basal unsupplemented diet contained about 4 times the the amount of pyridoxine required by chicks for normal growth The antipyridoxine effect of the linseed meal could be removed by mixing it with 3 times its weight of water allowing it to stand one day at room temperature and then drying it at 65° C No information was presented as to the possible nature of the interesting naturally-occurring antimetabolite

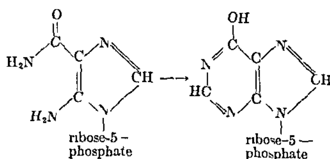
Antifolic Acid Compounds —The name 'folic acid" is commonly applied to pteroylglutamic acid (PGA), a member of the vitamin B complex group it is used in the treatment of certain anemias and other nutritional disturbances resulting from dietary deficiencies The chemical structure of PGA and certain antagonists of folic acid that will be considered are as follows



pteroylglutamic acid	R = OH	X = H
aminopterin	R = NH_2	X = H
10-methylpteroylglutamic acid	R = OH	X = CH_3
amethopterin (methotrexate)	R = NH_2	X = CH_3

PGA like other vitamins is widely distributed in biological materials in concentrations of only a few parts per million It may occur as the monoglutamate or conjugated with additional glutamic acid groupings in γ peptide linkage

Much evidence has accumulated from microbiological and enzyme studies that PGA is concerned in the biosynthesis of a number of amino acids including serine methionine and histidine and nucleic acid constituents including purine bases and thymine Isotope studies from many laboratories have established that the 'single carbon unit' is incorporated into these metabolites An 'incomplete purine ring " 4-amino-5-imidazole carboxamideribotide accumulates when *E coli* is grown with subinhibitory amounts of sulfonamide[35] or aminopterin (4-amino PGA)[36] This suggested[37] that folic acid or a derivative of it might be concerned in the actual transport of the single-carbon unit into the purine nucleus as follows



The discovery of the structure of the citrovorum factor (CF) as 5-formyl tetrahydrofolic acid further strengthened this concept for it appeared that CF was the coenzyme form of folic acid that participates in one carbon transfer reactions More recent studies have shown that the formyl group is on the 10-nitrogen atom and that either 10 formyltetrahydrofolic acid, or the closely related 5,10-methenyl-derivative, is the form of the folic acid coenzyme which functions in certain reactions of one carbon metabolism such as the incorporation of carbons 2 and 8 in purines It also appears that 10-hydroxymethyltetrahydrofolic acid (or the 5,10-methylene derivative) functions in the biogenesis of the 5-methyl group of thymine or the S-methyl group of methionine The enzyme hydroxymethyltetrahydrofolic dehydrogenase catalyzes the interconversion of these two functional forms of tetrahydrofolic acid,[38] thus providing a mechanism for the generation of either of these coenzymes depending on the state of reduction of the 1-carbon unit to be incorporated into a specific substrate Much is now known about the biogenesis of these functional forms of folic acid, this subject has been reviewed elsewhere [39] It is important to have an understanding of the chemical nature of the functional forms of folic acid and how they function in specific metabolic reactions for such knowledge makes it easier to understand how the folic acid antagonists may function in interrupting folic acid metabolism

It was found possible to alter the structure of folic acid in such a manner that compounds would result which would be antimetabolites of PGA Alteration of substituents on the pteridine moiety, the substitution of amino acids other than glutamate, and alkylation of the molecule are examples of approaches that were used

One of the first preparations having an action antagonistic to folic acid was "x-methyl PGA," which was synthesized by reacting *p* aminobenzoic acid with 2,4,5 triamino-6-hydroxypyrimidine and DL-brombutyraldehyde The crude compound when fed to animals produced symptoms typical of folic acid deficiency, including leukopenia, agranulocytosis, and anemia with hypoplastic bone marrow changes,[40] and teratogenic abnormalities in pregnant rats [41] All of these manifestations were reversed when adequate amounts of PGA were added to the diet Chemically pure methylated derivatives of PGA were later synthesized and their biological action was studied These compounds included 10-methyl, 9-methyl, and 9,10 dimethyl PGA Since functional forms of folic acid transport the one carbon unit via mechanisms involving the 10-nitrogen atom it is attractive to speculate that these later methylated derivatives of PGA function as antagonists either by blocking the formation of 10-formyl or 10-hydroxy-

methyltetrahydrofolic acid or their utilization by enzymes concerned in one carbon transfer

Derivatives of PGA in which the hydroxyl group in the 4 position of the pteridine was replaced by an amino group are potent antagonists of folic acid in a variety of biological systems Examples of such compounds are aminopterin and amethopterin Aminopterin was found to rapidly induce an acute folic acid deficiency in a number of experimental animals, but, in marked contrast to x-methyl PGA the toxicity of aminopterin for animals was not readily reversed by PGA However CF (citrovorum factor) reverses the toxicity of aminopterin in a wide variety of species[4]

Numerous studies with enzymes of bacterial and mammalian origin[43,44] have shown that CF is formed when PGA is incubated under anaerobic conditions with a formylating agent and the incubation mixture subsequently heated Aminopterin blocks this synthesis[45] It is now known that folic acid can be reduced to tetrahydrofolic acid by enzyme systems linked with reduced triphosphopyridine nucleotide as the electron donor,[46] and aminopterin is a potent inhibitor of these reduction steps[46,47] Since tetrahydrofolic acid rather than PGA appears to be the form of the vitamin that is required to accept a one carbon unit for subsequent formylation reactions, it can be seen that aminopterin in effect produces a folic acid deficiency by blocking the formation of the metabolically active form of the vitamin This latter point may be illustrated by considering recent studies of histidine metabolism in animals Rats on a diet deficient in folic acid excrete a heat labile substance which on heating gives rise to glutamic acid[48] the glutamate precursor was shown to be related to the histidine content of the diet[49] Subsequently the glutamate precursor was shown to be formiminoglutamic acid (FIGLU)[50] It is now known that histidine is catabolized by liver enzymes to FIGLU and that THFA is needed for the further degradation of FIGLU to glutamic acid ammonia and HCOOH[51,52] When urine from children with acute leukemia who were being treated with 4 aminofolic acid antagonists was examined, FIGLU was found to accumulate[53] thus supporting the view that the antagonists were inducing a folic acid deficiency by blocking the reduction of PGA to the functional form THFA needed for the disposition of FIGLU

The observed activity of the FA antagonists in depressing cytopoiesis in experimental animals led to the suggestion that the antagonists might be used in an attempt to modify blood dyscrasias which were marked by erythrocytosis or leukocytosis[54] The use of aminopterin in the treatment of acute leukemia in children was first described by Farber and associates[55] who reported that the antagonist produced beneficial effects and remissions in 10 of 16 cases receiving the drug These observations have since been confirmed by other investigations[56] Improvement has been noted in both the clinical and the hematological status although it may be of short duration The majority of cases show a reduction in the total leukocyte count Although the bone marrow rarely returns even temporarily to normal, the abolition of fever and the gain of weight together with reduction in the size of the lymph nodes and spleen and the control of the bleeding tendency are valuable clinical effects of the treatment However this use of aminopterin and related derivatives is subject to severe drawbacks in that the

remissions are only temporary and that the leukemic process appears to develop resistance to the antagonist The toxic symptoms of aminopterin in man include ulcerative stomatitis, gastric distress, nausea, vomiting, diarrhea, alopecia, and deafness The appearance of toxicity may be delayed and the toxic dose of drug exceeded before its action is evident, hence, the dosage employed is often less than that necessary for therapeutic efficacy CF can reverse the toxicity of the drug if given promptly[57] but, as might be expected, CF also reverses the pharmacological action of the antagonists [58]

Certain studies were reported[59] with a bearing on why the 4-aminofolic acid antagonists can bring about remissions in acute leukemia It was found[59a] that the folic acid content of leukemic cells was significantly higher than that of normal leukocytes, and that leukemic cells were more active metabolically in their ability to metabolize formate than normal cells [59b] Amethopterin effectively blocked the incorporation of formate by leukemic cells [59b] In harmony with these findings are experiments of Nichol[59c] who showed that leukemic cells have a marked capacity to form CF from PGA and that this process is vulnerable to the 4 aminofolic acid antagonists Recently halogenated derivatives of amethopterin have been synthesized[60] which in preliminary testing appear to be somewhat more effective than amethopterin in prolonging the survival time of mice with advanced leukemia [61]

There is good evidence that adult rats can obtain most or all of their folic acid requirements from the supply synthesized by their intestinal bacteria Omission of folic acid from purified diets given to rats in short term experiments was found to have no effect on reproductive performance or embryonic development,[62–63] but in longer term experiments a small incidence of hydrocephalus was noted in the offspring of rats which were on diets deficient in folic acid [66 67] The addition of sulfonamides to such purified diets has long been known to suppress the intestinal synthesis of certain vitamins, including folic acid, and by adding succinylsulfathiazole to purified diets deficient in folic acid resorptions were produced[6 63] and congenital abnormalities were observed in the young [64 65] Similar results, reversible by adding an appropriate level of folic acid, were produced when x-methyl PGA was added to the diet of rats [63–74] The abnormalities and their incidence with respect to the deficiency period are summarized in Tables 35 and 36 Their relation to the period of the gestation process during which the deficiency was imposed is also summarized in the tables Histological examination of the skeletal abnormalities showed that interference with the normal sequence of ossification had occurred together with retardation or absence of ossification, and deformed bones These findings indicate a role for folic acid in biological calcification Numerous anomalies were noted in the soft tissues including kidney hypoplasia with hydronephrosis, cardiovascular anomalies, defects in the diaphragm, hydrocephalus and eye abnormalities including cataract It was concluded by Nelson[32] that folic acid antimetabolites have a general teratogenic action in the rat While the mother is affected only slightly, if at all, she is completely unable to protect the fetus The known biochemical role of folic

acid in the synthesis of purines and pyrimidines logically leads to the conclusion that a lack of folic acid produces defects in normal mitosis which lead in turn to devastating effects upon the growth of the embryo

Analogous to the effects of x-methyl PGA which may be prevented by folic acid is the more powerful action of aminopterin (4-aminopteroyl glutamic acid) upon animals This action can be prevented not by folic acid but by citrovorum factor [4] Thiersch and Phillips,[75] reported that 0 3 to 0 45 mg when given by injection early in pregnancy to rats and mice

TABLE 43 —EFFECT OF MATERNAL PGA DEFICIENCY ON FETAL DEVELOPMENT IN RAT (NELSON[37])

Deficiency period (days)	*Resorptions*	*Per cent of litters*	*Abnormal young*
0 to 3 or 3 to 6 or 6 to 8 or 15 to 21	0	100	0
8 to 9 or 9 to 10	0	100	5
13 to 21	0	100	30
10 to 12 or 11 to 14 or 12 to 21	0	100	65 to 78
11 to 21	4	96	95
10 to 13	14	86	100
9 to 11	26	74	99
10 to 21	59	41	100
7 to 9 or 8 to 10 or 9 to 12 or 9 to 21 or 7 to 21 or 0 to 21	100	0	

TABLE 44 —PER CENT INCIDENCE OF MACROSCOPIC FETAL ABNORMALITIES IN RATS OBSERVED IN MATERNAL PGA DEFICIENCY INDUCED BY X METHYL PGA (NELSON[52])

Deficiency period (days)	*Edema and anemia*	*Cleft palate*	*Club foot*	*Kidney defects*	*Gonad defects*	*Cardio-vascular defects*
12 to 21	90	*		*		
11 to 21	95	99	77	100	6	
11 to 14		48	17			
10 to 21	100	100	100	100	85	22
10 to 13	*	100	94	66	51	29
10 to 12	*	60	54	11	7	30
9 to 11		86	62	49	21	56

* To a minor extent or in low incidence

maintained on a stock diet invariably resulted in fetal death, and that embryonic mesenchyme was the tissue which was primarily affected The dosage used was not sufficient to produce seriously toxic effects on the mothers The oral administration of 8 to 15 mg of aminopterin during the first trimester of pregnancy in women was studied by Thiersch [76] who found that fetal death followed by spontaneous abortion occurred in 10 or 12 treated cases Congenital malformations of the cranium or of the face were noted in 3 older fetuses

Avidin.—One of the early observations of a specific nutritional deficiency in experimental animals was made by Boas,[77] who described an abnormal condition in rats which was produced by adding raw egg white to the diet. The animals grew slowly and developed scaly dermatitis with extensive loss of hair and a thickening of the eyelids. The apparently toxic nature of the egg white was removed by cooking or could be "neutralized" by adding large amounts of yeast to the diet. It is now known that egg white contains a specific protein "avidin," which combines with biotin and prevents this vitamin from entering the blood stream when present in the intestinal tract. Avidin is denatured by heat and its power of combining with biotin is limited, thus accounting for the observation that the effect of raw egg white in the diet may be overcome by adding yeast to increase the biotin level in the diet. One may speculate that avidin may help to protect eggs against bacterial spoilage by inhibiting the growth of bacteria in the egg white which need biotin, while at the same time the yolk is a comparatively rich source of biotin which enables the chick embryo to grow without encountering a deficiency of this vitamin. Curiously enough the chick after hatching may readily be brought into a state of biotin deficiency by adding raw egg white to the diet.

Biotin deficiency was produced by Sydenstricker and coworkers[78] by feeding a diet in which approximately 30 per cent of the total calories was supplied by desiccated egg white. During the third and fourth weeks, all 4 human subjects developed a fine scaly desquamation which disappeared about a week later. A pronounced greyish pallor of the skin and mucous membranes was noted during the seventh and eighth weeks together with atrophy of the lingual papillæ. Dryness of the skin and desquamation returned during the ninth and tenth weeks and depression, muscle pains, precordial distress and anorexia were noted. These symptoms disappeared when a biotin concentrate was injected and the skin and mucous membranes returned to normal color.

Avidin is not an antimetabolite of biotin in the strict sense of the term, but it induces the deficiency by interfering with the uptake of the vitamin from the gut. A number of synthetic analogs of biotin have been shown to function as metabolic antagonists. Desthiobiotin has antibiotin activity for chicks but can replace biotin for the growth of yeast. One of the most potent antagonists of biotin for microorganisms is γ-3,4-ureylene cyclohexyl butyric acid, one of a group of compounds synthezised by English and coworkers.[79] No effects on animals have been reported for this group of compounds.

Triethylcholine.—A deficiency of choline leads to various nutritional disturbances in animals including fatty livers, hemorrhagic kidneys and perosis in birds. In addition, choline functions as a source of labile methyl as shown by its ability to restore growth in animals on methionine-deficient diets containing homocystine. Choline has a dual nutritional function, for it appears that it is important as an intact molecule in the formation of lecithin and that it may supply labile methyl groups probably after a preliminary oxidation. The ethyl analog of choline, triethylcholine, appears to be incapable of supplying labile methyl but it has a lipotropic effect[80] and it prevents renal hemorrhages when fed at low levels. When

fed at higher levels, triethylcholine produces markedly toxic signs which include muscular weakness, exophthalmos and convulsions followed by death. The toxicity is prevented by choline[81] leading to the suggestion that triethylcholine blocks the formation of acetylcholine. It has been demonstrated that triethylcholine may be incorporated into phospholipids[8] and this finding would help to explain its lipotropic effect.

Glucoascorbic Acid.—The addition of 10 per cent of glucoascorbic acid was found[83] to produce a syndrome in cotton rats and mice characterized by slow growth, severe diarrhea and tissue hemorrhages. It was concluded that the syndrome was analogous to scurvy as observed in other species, but the simultaneous administration of ascorbic acid did not prevent or cure the disease in mice and rats. Instead, a constituent of natural foodstuffs such as grass, cabbage and liver was found to prevent the toxic effects of glucoascorbic acid. The protective substance was different in its properties from ascorbic acid.[84] A disease was also produced in guinea pigs by feeding glucoascorbic acid as a supplement to a purified diet, and in this case the disease was prevented by 1 mg. of ascorbic acid daily.[8] The condition produced in the guinea pigs was not typical of vitamin C deficiency, so that there is some question as to whether glucoascorbic acid is actually an antimetabolite of ascorbic acid[7] because the syndrome produced by glucoascorbic acid differs from true scurvy and is not consistently reversible by ascorbic acid.

Riboflavin Antagonists.—Two analogs of riboflavin, *isoriboflavin* and the phenazine analog were found to produce a mild riboflavin deficiency in rats which was reversed by riboflavin.[86,87] A third analog, galactoflavin, was studied by Emerson and coworkers[88] and was found to depress growth and increase mortality. The effects were almost completely counteracted by feeding an excess of riboflavin. Further studies with galactoflavin and isoriboflavin[89] showed that regression of lymphosarcoma implants occurred in mice which were rendered temporarily deficient in riboflavin, either by the feeding of a diet low in riboflavin or by the administration of one of the antagonists. The anti-tumor effect of the antagonists did not appear to differ from the similar effect produced by a simple dietary deficiency of riboflavin.

Dicumarol and Related Compounds.—A hemorrhagic disease in cattle was found by Schofield[90] to occur when the animals consumed spoiled sweet clover. The substance responsible for the disease was isolated and identified by Link and his coworkers[91] as 3,3′-methylenebis(—4-hydroxycoumarin) or "Dicumarol." The hemorrhagic disease was caused by a depression of the production of prothrombin and the hypoprothrombinemia was reversed by vitamin K.

A large number of compounds chemically related to Dicumarol have been found to have hypoprothrombinemogenic properties.[6] Some of these compounds are used in medicine to inhibit intravascular blood clotting in coronary disease and other conditions characterized by the formation of thrombi. The biological antagonism between vitamin K and Dicumarol has been discussed and studied by James *et al.*[92] and by Miller *et al.*[93] who noted that vitamin K_1 is more active as an antagonist of Dicumarol than are certain of the vitamin K analogs.

ANTAGONISTS OF AMINO ACIDS

Methionine Antagonists.—Methionine has several important functions in nutrition and metabolism. It is one of the indispensable amino acids needed in the diet for the formation of body proteins, it functions as a source of methyl groups for the synthesis of creatine and other methylated metabolites, and it can be converted into cystine, another indispensable amino acid, in the body. Methionine deficiency in animals produces hepatic necrosis and other serious disturbances.

The S-ethyl analog of methionine, ethionine, prepared synthetically, has been found to be a compound of much nutritional interest. The first studies[94] showed that it produced a toxic effect in rats on diets low in methionine. The depression of growth was partially reversed by adding methionine to the diet. Somewhat paradoxically, ethionine was found to prevent fatty livers and hemorrhagic kidneys in rats on diets deficient in both choline and methionine.[95] It is conceivable that this effect could be due to the formation of triethylcholine from ethionine. Methionine is believed to proceed to the formation of choline by conversion to S-adenosyl methionine in which the methyl group is "labilized" for transfer to amino ethanol, thus leading to the formation of choline. By an analogous procedure ethionine might be converted to S-adenosyl ethionine which could result in the formation of triethylcholine. This substance, although toxic, is known to have a lipotropic action.

Farber and coworkers[96] employed different experimental conditions from those used by Hardwick and Winzler and reported that ethionine was capable of inducing fatty livers in fasted female rats. Choline and other lipotropic agents had little or no effect upon this type of fatty liver which was prevented by large doses of carbohydrates or by methionine so that in their experiments ethionine appeared to be functioning as a specific antagonist of methionine rather than as a possible precursor of a choline-like substance. Another investigation[97] described the inhibition of growth of rats by ethionine when added to a diet containing 25 per cent casein. The inhibition was reversed by methionine or choline, but cystine and homocystine were ineffective. The authors concluded that ethionine had increased the requirement for choline. Perhaps here again we are confronted with the formation of triethylcholine.

The effect of ethionine upon the incorporation of methionine and glycine into the proteins of growing rats was studied by Simpson and coworkers.[98] Inhibition in the uptake of these amino acids in the tissue proteins was observed, and the inhibition was reversed by methionine. Ethionine also inhibited the conversion of methionine to cystine in intact rats.

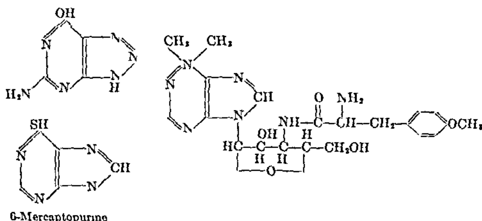
It is thus evident that ethionine produces several effects upon metabolism in experimental animals. It interferes with methylation, with the synthesis of proteins, with the conversion of methionine to cystine and with the lipotropic action of methionine. These findings reflect the complex role of methionine in metabolic processes. Ethionine also appears to decrease the formation of certain enzymes in rats, including tryptophane peroxidase,[99] and appears to inhibit the activity of choline oxidase and sarcosine oxidase in rat liver homogenates.[100]

Other antagonists of methionine which have been studied include methoxinine,[101] methionine sulfoxide and methionine sulfoximine. The latter two compounds are antagonists of glutamic acid and glutamine; indeed, methionine sulfoxide may actually replace methionine in the prevention of anemia in rats,[102] but it competitively inhibits the enzymatic production of glutamine from glutamic acid.

Of considerable nutritional interest is a toxic principle produced in plant proteins by treatment with nitrogen trichloride, as in the "agenizing" process in bleaching wheat flour, and which produces "running fits" (canine hysteria) in dogs. The toxic agent is an oxidized derivative of methionine,[103, 104] a sulphoximine, and its toxic effects are reversed by methionine.[105]

ANTAGONISTS OF PURINES AND PYRIMIDINES

The purines and pyrimidines are the building blocks of the nucleic acids in the nuclei of all living cells. Since the growth of parasitic tissues is accompanied by a rapid synthesis of nucleic acids, agents which would interfere with nucleic acid metabolism might be potentially useful as chemotherapeutic agents. It is not surprising therefore that many analogues of purines or pyrimidines have been prepared and studied for their effect on nucleic acid metabolism. This has been one of the major approaches to the chemotherapy of cancer. Representative examples of antimetabolites will be discussed from the viewpoint of their metabolic effects; for a more detailed treatment of this subject several excellent reviews are available.[106, 107]



6-Mercaptopurine

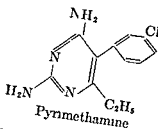
Examples of purine analogues which appear to block the utilization of purine bases for nucleic acid synthesis

A number of analogues of the purine bases have been prepared which appear to be true antimetabolites of purines in that their effects in certain biological systems can be reversed with purine bases. Such data imply that the antimetabolite is interfering with the utilization of the purine base for incorporation into nucleic acid. One of the first of such antimetabolites to be synthesized which created wide interest was 8-azagua-

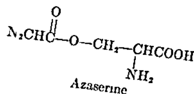
nine[108] wherein the 8-carbon atom was replaced by a nitrogen atom. This analogue, although but moderately inhibitory to bacteria, was found to be extremely toxic to the protozoon *Tetrahymena geleii*.[108] The growth inhibition could be relieved by guanine. 8-Azaguanine has been found to effectively inhibit the growth of a number of experimentally induced tumors in mice and rabbits, but has not been effective in acute leukemia.

An important purine analogue, which was synthesized by Elion *et al.*[109] is 6-mercaptopurine (6-MP). It bears a structural relationship to adenine in that the 6-amino group of adenine is replaced by thiol. The toxicity of 6-MP for lactic acid bacteria may be reversed by suitable additions of the various purines, and from these and other considerations Elion *et al.*[110] postulated that 6-MP may interfere primarily with the conversion of adenine to guanine, presumably this interference occurs at the nucleotide level. In this regard it is interesting to note that Goldin found that 20 times as much adenine was required to reverse the lethal effects of 6-MP in mice as adenylic acid.[111] Other pharmacological effects of 6-MP in various animals species have been reported by Philips.[112] 6-MP has proved to be a useful drug in cancer chemotherapy, particularly in the treatment of acute leukemia. Moreover it may be effective in those instances where the patient is resistant to treatment with folic acid antagonists. This is logical from a biochemical viewpoint since the two antimetabolites have been demonstrated to function at different biochemical loci in interfering with purine metabolism. A thorough appraisal of the clinical status of 6-MP has appeared.[113]

The antibiotic Puromycin is a particularly interesting antimetabolite, since it is naturally occurring. Amino-nucleoside, which is Puromycin without the 3′-p-methoxyl-L-phenylalanyl moiety, and which can be prepared synthetically, is inhibitory for certain trypanosomes and the inhibition is relieved by adenine.[114] Although these drugs have not been particularly useful in cancer chemotherapy, Puromycin has been shown to have amebicidal activity. The finding that Puromycin contained an amino sugar has stimulated considerable synthetic work in which known purine bases or analogs have been prepared with this or related amino sugars.



Pyrimethamine



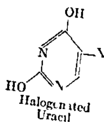
Azaserine

Examples of antimetabolites that interfere with the de novo synthesis of purines

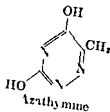
A number of years ago Hitchings *et al.* prepared a number of 2,4-diaminopyrimidines and found that such compounds were folic acid antagonists for *Lactobacillus casei*.[115] Extensive studies of the effect of various substituents on the 2,4-diaminopyrimidine structure ultimately led to structures which were potent antibacterial and antimalarial agents.[116] 5-p-chloro-

phenyl 2 4 diamino-6-ethyl pyrimidine (Pyrimethamine) for example, was found to be approximately 1000 times as potent as quinine as an antimalarial The toxicity of pyrimethamine for *Leuconostoc citrovorum* (*Pediococcus cerevisiae*) is reversed competitively by citrovorum factor (CF 5-formyl 5 6 7 8 tetrahydrofolic acid) with *Streptococcus faecalis* CF was more effective than folic acid in reversing the toxic action of this pyrimidine from which it was suggested that the pyrimidine may block the conversion of folic acid to CF [117] When pyrimethamine was fed to rats, toxic symptoms suggestive of a folic acid deficiency developed, these symptoms were partially reversed by administering CF in the diet [117] It is apparent that both pyrimethamine and Aminopterin are 2,4 diamino-pyrimidines and it seems likely from the biological activity of pyrimethamine that it may also function similarly to the 4 aminofolic acid antagonists in blocking the conversion of folic acid to tetrahydrofolic acid Thus pyrimethamine might be expected to indirectly block the *de novo* synthesis of purines and thymine at those points where THFA is known to function

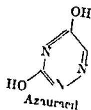
Azaserine (O diazoacetyl L-serine) is another example of an antibiotic that appears to function as an antimetabolite it was isolated from a streptomycin culture [118] Enzyme studies established that one reason for the toxicity of azaserine in biological systems is because it interferes with the metabolism of glutamine whose structure it superficially resembles Hartman Levenberg and Buchanan[119] in their studies of the synthesis of inosinic acid from glycine in a pigeon liver enzyme system found that azaserine blocked synthesis of the nucleotide with the accumulation of glycinamide ribotide or its formyl derivative The effect of azaserine was counteracted by glutamine from which it appeared that azaserine was interfering with the ability of glutamine to form formylglycinamidine ribotide necessary for the subsequent steps in inosinic acid biosynthesis Azaserine has been extensively studied in a variety of experimental neoplasms and in man but it appears to be of no practical value in the treatment of cancer



Halogenated Uracil



Azathymine



Azauracil

Examples of pyrimidine analogs which interfere with pyrimidine metabolism

Considerable research has also been directed towards fashioning analogues of the pyrimidine bases particularly uracil and thymine, in an attempt to obtain compounds which might interfere either with the synthesis or utilization of these bases needed for nucleic acid synthesis Much is now known about the pathway of pyrimidine nucleotide synthesis in animals cells and such information has further stimulated the preparation of antimetabolites that might possibly interfere with this pathway The probable route of uridine nucleotide (uracil ribotide) biosynthesis is summarized

briefly as follows aspartic acid ⟶ carbamylaspartic acid ⟶ 5,6-dihydroorotic acid ⟶ orotic acid ⟶ orotidine-5′ phosphate ⟶ uridine-5′phosphate ⟶ ribose nucleic acid Uracil itself may also be incorporated into RNA presumably by first being converted to uridine-5′-phosphate Thymidine or thymidylic acid required for DNA synthesis, may also be derived via the above orotic acid pathway It has been shown that deoxyuridine (arising from dehydrogenation of uridine) or deoxyuridylic acid may accept a one carbon unit from tetrahydrofolic acid giving rise to thymidine or thymidylic acid

Some of the first analogues of uracil that were prepared having interesting biological activity were 5-bromouracil, 5-chlorouracil and 5-nitrouracil [170] 5-bromouracil for example blocked the utilization of thymine by *Lactobacillus casei* The 5-fluoro derivative has only recently been prepared[171] and found to be more than 500 times as active in inhibiting growth of *Lactobacillus leichmanii* as 5-bromouracil 5-fluorouracil has been found to be very active in inhibiting growth of a number of transplanted tumors[172] and its effects on nucleic acid metabolism have been studied in great detail [173] These studies have shown that fluorouracil inhibits the conversion of uracil or orotic into RNA uracil, it inhibits the methylation reaction leading to thymidine or thymidylic acid, evidence was also presented that fluorouracil itself could be incorporated into nucleic acid thus leading to an altered nucleic acid which presumably would be non functional

Another important analogue of uracil is azauracil in which the 6-carbon atom of uracil is replaced by a nitrogen atom, this analogue has been studied by Welch and his collaborators [106,174] Azauracil inhibits the growth of certain lactobacilli and the toxicity may be reversed competitively by uracil, indicating that the inhibitor interferes with the utilization of uracil The analogue also inhibits the growth of certain neoplasms in the mouse These studies led to the preparation of azathymidine and an investigation of its biological activity, since it might be anticipated that an appropriate analogue of thymine might interrupt DNA synthesis Azathymine, like azauracil, is inhibitory for a number of lactobacilli, from such studies it was discovered that *S faecalis* converts azathymine to the deoxyriboside,[175] which probably is the active inhibitor Azathymidine has been prepared by this means, *i e*, enzymatic deoxyribosidation of azathymine, studies of the inhibitory action of azathymidine are particularly interesting because it has been shown that in certain mammalian cells azathymidine interferes with the incorporation of C^{14} formate into the thymine of DNA [106]

ANTITHYROID SUBSTANCES

Certain plants, particularly in the *Cruciferæ*,[126] but also including soybeans,[127] contain substances which depress the uptake of iodine by the thyroid gland The production of thyroid hormone is consequently diminished and signs of goiter will appear if such substances, 'goitrogens' are ingested for prolonged periods Most of the studies in this field have been carried out with synthetic rather than natural goitrogens The synthetic agents include the sulfonamides[128] and the thioureas and thiouracil [129,130] Thiou-

racil and more recently propylthiouracil have come into wide clinical use in the treatment of all types of hyperthyroidism, whether represented by diffuse or by nodular goiters and regardless of the number of nodules. As might be expected, thiouracil is of no value in the treatment of simple goiters.

The potency of goitrogens may be readily and rapidly estimated by measuring their effect in depressing the uptake of a tracer dose of radioactive iodine (I^{131}) by the thyroid gland. The measurement may be carried out by placing an external Geiger counter in contact with the gland of the living subject or, more accurately, by excising the gland postmortem in rats a few hours after administering the tracer dose of I^{131}.

A natural goitrogen was isolated from cabbage by Astwood and co-workers[131] and was shown to be L-5-vinyl-2 thiooxazolidone.

The goitrogens are not true antimetabolites of thyroxine since they inhibit its synthesis rather than its action. A series of analogs of thyroxine has been synthesized and found to have antithyroxine activity. Compounds in this series include ethers of N-acetyldiiodotyrosine,[132] O-benzyldiiodotyrosine[133] and iodinated phenyloxyacetic acids.[134]

The effect of thiouracil on nutrition is so profound that many investigators have used it to modify the growth of farm animals. Muhrer and Hogan[135] in paired feeding experiments with swine lasting twenty-eight days, found that the rate of gain with thiouracil was 2.1 lb. per day as compared with 1.4 lb. for untreated controls and corresponding improvements were noted in the efficiency of food utilization by the supplemented pigs. The supplemented pigs were wider and shorter and appeared fatter than the controls but subsequent work showed a slight decrease of the fat percentage of the carcass and a slight increase in water content.[136] Less marked differences between supplemented and control animals were noted when *ad libitum* feeding was employed but again there was a marked improvement in feed conversion.[137] If the goitrogen is given at an early age the pigs show greatly reduced gains accompanied by signs of cretinism or myxedema.[138] The increased efficiency of feed utilization obtained with thiouracil is readily explained by the depression in thyroid function with a consequent lowering of heat production by the animals.[139]

The feeding of goitrogens increases thyroid weight and induces hypothyroidism in chicks[140] and thiouracil has been used to produce an increase in fat deposition and in market grade of chickens. There is a notable increase in the fat content of the skin of such birds.[141]

CONCLUSION

Roblin[14] has drawn attention to pitfalls which may arise in the use of antimetabolites in metabolic studies because of the complex nature of many of the biochemical antagonisms in living cells. The value of antimetabolite studies in nutrition is to provide leads which should be reinforced with other biochemical studies including the use of isotopes. With a few notable exceptions, the antimetabolites have been of less chemotherapeutic value than was anticipated in the early days of this field of in-

vestigation The antimetabolites, nevertheless, are of great value in studies of the biochemical processes which underlie nutrition

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Many coenzymes, however, are only loosely bound and the enzyme is isolated as the apoenzyme. A differentiation between a prosthetic group, such as the iron-porphyrin of the cytochromes, and a coenzyme, such as diphosphopyridine nucleotide, is usually made on the ease of dissociation of the compound from the apoenzyme, prosthetic groups having very low dissociation constants.

The term cofactor is more general than coenzyme. Where the function of a compound which is required in an enzymatic reaction is not clearly understood, it is usually termed a cofactor rather than a coenzyme. Thus, biotin and vitamin B_{12} which activate some reactions, are cofactors since their mode of action has not been determined. Inorganic cations and anions are often required in enzyme catalyzed reactions and are classed as cofactors. In fact, trace minerals are found in many crystalline enzymes and are absolutely required for the enzyme's activity, but their role in the enzymatic reaction is not as well understood as that of some of the coenzymes.

TABLE 45.—VITAMIN—COENZYME RELATIONSHIPS

Vitamin	*Coenzyme*	*Enzyme Reactions*	*Ref*
Nicotinic acid	Di and Triphosphopyridine nucleotides	Dehydrogenase reactions (*i e* glucose-6-phosphate, isocitrate malic, alcohol, lactic, glyceraldehyde phosphate, etc dehydrogenase)	(5)
Riboflavin	Flavinadenine dinucleotide and flavin mononucleotide	Amino acid oxidases, cytochrome c reductases, succinic dehydrogenase xanthine oxidase and glycolic oxidase	(5)
Thiamine	Thiamine pyrophosphate (cocarboxylase)	Oxidative decarboxylation of pyruvic and α ketoglutaric acid	(6)
Pyridoxine	Pyridoxal phosphate Pyridoxamine phosphate	Transaminases and amino acid decarboxylase	(5)
Pantothenic acid	Coenzyme A	Acetylation reactions (fatty acid metabolism, formation of citrate from pyruvate and oxalacetate)	(7)
Biotin	(not identified)	Carboxylation and decarboxylation reactions	(8)
Folic acid	(Tetrahydrofolic acid)	Biosynthesis of purines	(9, 10)
B_{12}	(not identified)	Biosynthesis of purines and proteins	(10, 11)
Ascorbic acid	(not identified)	Oxidation of tyrosine	(12)

Relationship Between Vitamins and Enzymes.—Some cofactors and coenzymes are now recognized to contain vitamins often as relatively simple compounds with purines or pyrimidines, and on occasion as chelation products with trace minerals.[4] With the discovery of each new vitamin a specific role as a coenzyme has been sought. In Table 45 are listed the vitamins which have been shown to function as coenzymes and the enzymatic reactions in which they are involved. In many cases the

coenzyme appears to be the only bound form of the vitamin, and their nutritional requirement has been explained on the basis of their coenzymatic function. It is important to recognize that though the vitamin may contribute to the structure of only one or two coenzymes, the coenzymes themselves may be active in many systems depending on the nature of the apoenzyme with which they combine. Thus though riboflavin is a portion of only flavin mono- and dinucleotide, approximately thirty flavoprotein enzymes are now known. Many of the cellular reactions which involve vitamin containing coenzymes have been fairly well charted but there are still large gaps in our knowledge not only as to the requirement but also as to the role of these coenzymes.

Two of the vitamins listed in Table 45 function in the terminal electron transport system (*i.e.* cytochrome system) which mediates the oxidation of a number of cellular metabolites by molecular oxygen. These are riboflavin in the cytochrome *c* reductases and nicotinic acid in the pyridine nucleotides. Recently, vitamin E[13] and vitamin K[14] have also been suggested as participating in this system. Vitamin K may be required in the coupled phosphorylations which occur concomitantly with the transfer of reducing equivalents from substrate to oxygen by the electron transport chain. However, the mode of action of vitamins K and E has not been determined, whereas it is known that nicotinic acid and riboflavin function as electron carriers in this system, being cyclically reduced and oxidized.

Burch *et al*[15] and Chaloupka *et al*[16] have studied the requirement of nicotinic acid to maintain blood levels of pyridine nucleotides in rats. The former authors have shown that on a nicotinic acid and tryptophan deficient diet the diphosphopyridine nucleotide levels of the erythrocytes, leukocytes and liver decrease but not to the same extent. Supplementing the diet with nicotinic acid or nicotinamide maintains the diphosphopyridine nucleotide level of the blood at normal values, but L-tryptophan, a precursor for the *in vivo* synthesis of nicotinamide, only partially restores the pyridine nucleotide levels. If the rat can be used as a guide, these authors propose that the concentration of pyridine nucleotide in erythrocytes of man may serve as a measure of moderate to severe nicotinic acid deficiency. However, since human red cells contain much less pyridine nucleotide than the rat, it will be difficult to determine the value of this test until actual studies are made in man on restricted uptakes.[15]

Peters in 1936[17] demonstrated that there is a decreased pyruvic acid oxidation in brain slices from thiamine deficient animals. The decreased capacity of the slice could be raised to the normal level by addition *in vitro* of thiamine or thiamine pyrophosphate. The results of Dalgliesh[18] indicate that thiamine but not biotin is involved in tryptophan metabolism. Arnstein[19] has summarized the effect of folic acid deficiency on the metabolism of one-carbon units and related compounds which are involved in nucleic acid metabolism. In the rat the oxidation of methyl groups to carbon dioxide is not significantly altered, but the oxidation of glycine, glyoxylic acid, formate and choline are decreased.

The effect of dietary restriction of riboflavin on flavoenzymes of different tissues has been studied.[19, 20] The content of flavin adenine dinucleotide and flavin mononucleotide of the livers of rats on a riboflavin deficient diet

differ appreciably in the rate and extent of depletion, the mononucleotide generally disappears more rapidly.[19] The heart and kidney are more resistant to depletion than the liver, and in the brain there is no significant change in either coenzyme. In the normal animal, the activities of the various flavoenzymes differ greatly from organ to organ with levels of activity highest in the liver and kidney, intermediate in heart, and lowest in brain. On the deficient diet there are negligible changes in the flavoenzyme content of the brain of rats. Of the hepatic enzymes tested, only D-amino acid oxidase, xanthine oxidase, and glycolic oxidase were appreciably decreased, whereas pyridine nucleotide dehydrogenase, a flavoenzyme also, was only slightly affected even with severe riboflavin deficiency. One of the most significant features of this study, as pointed out by the authors is the range in sensitivity of the various flavoenzymes and the differences in the effect of deficiency in the tissues studied. Within six weeks glycol oxidase of the liver was reduced 92 per cent of the control but pyridin nucleotide dehydrogenase only about 10 per cent. These findings indicate the potential pitfalls of assaying only one enzyme or tissue, and should be a guide for future investigations of this nature.

The investigations of Keith *et al.*[1] and Westerfeld and Richert[20] indicate another difficulty in the extrapolation of the results of enzyme studies in experimental animals to those of studies of man. It has been demonstrated that chickens with adequate folic acid have a lower hepatic xanthine oxidase than those on a folic acid deficient diet,[21] but, in the rat, the folic acid content of the diet has little or no effect on hepatic xanthine oxidase.[22] Thus, because of potential species differences in the effect of various vitamins on specific enzymes of the cell, extrapolation of the results with experimental animals to those of human nutrition is very uncertain.

In studies of the effect of dietary vitamin intake on cellular levels of oxidative enzymes, one must also consider the complex interplay of vitamins and protein metabolism because a deficiency of one vitamin will often cause changes in the activity of an enzyme system where there is no apparent relationship between the vitamin and a required coenzyme.

Relationship of Dietary Protein and Amino Acids.—A number of studies have been carried out to determine the effect of dietary protein or amino acid intake on the concentration of plasma and cellular enzymes. Since enzymes are themselves proteins it can be expected that they will participate to some degree in the dynamic equilibrium of protein metabolism. The activity of some thirty odd enzymes has been measured in experimental animals on a protein deficient diet. Hepatic xanthine oxidase,[3-25] catalase,[23] D-amino acid oxidase,[26] arginase[23-26] alkaline phosphatase and cathepsin[3] of the rat are very susceptible to low or non protein dietary intakes. D-amino acid oxidase and arginase activity[6] are lost faster than the decrease of general liver protein. As with vitamin deficiencies, there are, however, marked differences between tissues, e.g., the liver D-amino acid oxidase is sensitive to the level of protein or amino acids in the diet, but kidney D-amino acid oxidase is unaffected.[27] Cytochrome oxidase activity has been reported to decrease in livers of rats on a protein deficient diet, but evidence to the contrary has been presented. Potter and Klug[8] have observed a decreased hepatic succinoxidase activity of rats on a low protein

and a high fat or carbohydrate diet. Acute starvation experiments with rats have demonstrated that liver and in some cases kidney enzymes are decreased, but the rate of change depends upon the individual enzyme. This loss of enzyme activity may be due to either a decreased rate of synthesis or a more rapid destruction of the enzyme. In either case, some enzymes apparently participate in the general metabolic protein pools of the body. It is difficult and perhaps meaningless to extrapolate these acute starvation experiments with animals to the chronic prolonged undernutrition occurring in man.

The effect of specific amino acid deficiencies on various enzymes has been studied.[29–35] With rats on a diet deficient in either tryptophan, isoleucine or phenylalanine, the enzymes arginase, aconitase and D amino acid oxidase of the kidney and liver do not change, whereas catalase and xanthine oxidase decrease irrespective of the maintenance of liver nitrogen by forced feeding.[29] Prigmore *et al.*[30] have studied the efficiency of diets lacking histidine, lysine or methionine in restoring various hepatic enzymes of the rat which were depleted by non-protein diets. Histidine is not required for the restoration of xanthine oxidase nor methionine for succinic oxidase. Choline oxidase can be restored by diets deficient in all three of the above mentioned amino acids.

Up to rather recent times studies of the changes in enzyme activity of human subjects in malnutrition have been limited because only one tissue, blood, was readily available. With the development of relatively innocuous techniques for liver biopsy, measurements of the changes in enzyme content of livers of humans, particularly with kwashiorkor and nutritional edema, have been carried out.[1–3] On thirty children with kwashiorkor, Waterlow and Patrick[1] have found variable results in the measurement of several dehydrogenases and succinoxidase activity of liver biopsies before and after treatment. Xanthine and D amino acid oxidase were significantly decreased in the livers of kwashiorkor patients both on a weight basis and per unit of protein. In rat livers these two enzymes have also been shown to be particularly susceptible to protein deficiencies. Cytochrome c reductase, cytochrome oxidase, lactic dehydrogenase, malic dehydrogenase, succinic dehydrogenase, glycolic acid oxidase and transaminase were not significantly reduced when calculated per unit of protein.[2] In contrast, catalase and alkaline phosphatase activity have been found to be higher in protein deficient patients;[3] the former increased activity may be due to a higher iron content of the liver of these patients before treatment. It is very difficult to evaluate these results with human subjects because in most cases, patients suffering from malnutrition due to a low protein diet are frequently deficient in vitamins or minerals.

The results of these studies on man and experimental animals indicate that those enzymes whose concentrations are critical for cellular metabolism, such as cytochrome-c-reductase, are not greatly affected by protein deficiency. Apparently the cell is capable of sparing those enzymes whose functions are absolutely necessary for cellular maintenance.

Relationship of Trace Elements.—It has been amply demonstrated that some enzymatic reactions require the presence of inorganic anions or cations for maximal activity and in fact a number of enzymes have been isolated

which contain a metal in a bound form. In Table 46 are listed some of the known metal-requiring oxidative enzymes. Both pyridine nucleotide-cytochrome c reductase and succinic dehydrogenase also contain flavin and are now classed as metallo-flavoenzymes.[37] McElroy has reviewed the role of trace elements in enzyme systems.[38]

TABLE 46.—METALLO-OXIDATIVE ENZYMES

(See Dixon and Webb[36] for specific references)

Metal	*Enzyme*
Iron	Pyridine nucleotide cytochrome c reductases
	Succinic dehydrogenase
Iron–porphyrin	Peroxidase
	Catalase
	Cytochromes
Copper	Butyrl-CoA dehydrogenase
	Ascorbic acid oxidase
	o-Diphenol oxidases
	Uric acid oxidase
Zinc	Alcohol dehydrogenase
	Lactic acid dehydrogenase
	Glutamic acid dehydrogenase
	Phosphoglyceraldehyde dehydrogenase
Molybdenum	Xanthine oxidase
	Aldehyde oxidase
	Nitrate reductase

Through the pioneering work of McCollum[39] the requirement for trace minerals in the diets of animals is now well established. A number of elements have been detected in animal tissues and fluids, but the biological role of metals such as nickel and aluminum has not been determined. The study of the changes in enzyme systems in animals on a mineral deficient diet has proven particularly difficult for two reasons, (*a*) many of these minerals are required in such limited quantities that it is difficult to prepare diets free of the metal and (*b*) it is nearly impossible to deplete the cellular stores of some of these metals. Thus, though copper has been demonstrated to be an important micronutrient in animals, its deficiency in human adults has never been recognized.[40]

Van Reen and Pearson[41] have shown that with a magnesium deficiency in ducklings there is a decrease in alkaline phosphatase and diphosphopyridine nucleotidase activity in the brain, but cytochrome oxidase is unaffected. The addition to the diet of small quantities of magnesium corrected the abnormalities in these enzymes. Westerfeld and Richert[42] found that liver and intestinal xanthine oxidase of the rat varied with the diet offered. Diets containing soy bean and liver were rich in an active principle required for maintenance of the xanthine oxidase activity, which was subsequently identified as molybdenum.[43] The cytochrome oxidase activity of liver, heart and bone marrow in the rat is greatly reduced under conditions of copper deficiency.[44,45] Though copper has been reported to be present in cytochrome oxidase, the decreased enzymatic activity may

be related to its hematopoietic activity The catalase activity of liver and kidney is also decreased, but unexplainably that of heart is increased

With diets containing an excess of zinc there is a reduction in liver catalase and cytochrome oxidase activity Addition of copper to the diet resulted in an increase in both enzymes, but did not correct the growth inhibition produced by zinc [46] Excess molybdenum increases liver alkaline phosphatase which is counteracted by feeding of copper or various sulfur containing compounds (methionine, cysteine, sodium thiosulfate and sodium sulfate) [47] Cunningham[48] has discussed the interrelationship of copper and molybdenum and concludes "that these elements are reciprocally antagonistic in animal metabolism" Thus, mineral nutrition has its share of complex and imperfectly understood relationships

Conclusion —This brief review has indicated some of the current approaches in the study of the effect of dietary intake on cellular metabolism Some of these relationships are now understood, but there are large conspicuous gaps in our present knowledge As an example very little is known of the enzymatic changes that occur with variations in the fat content of the diet Recently there have been reports that with low fat diets there is an increase in the cytochrome oxidase activity of the liver[49] and a decrease in the efficiency of oxidative phosphorylation [50] This latter effect may be due to an alteration of the mitochondrial structure rather than a direct affect on the enzyme system It is possible that a deficiency of a dietary constituent, such as fat or protein, may alter the structure of the cell and cellular inclusions in such a manner as to change the enzymatic activity of the cell

The enzymatic analysis of liver biopsy material in clinical chemistry may be a useful tool in the diagnosis of not only dietary deficiencies but also other metabolic disorders This technique may be more sensitive than the current liver function tests One should bear in mind however, that enzyme activities as measured in artificial *in vitro* systems may be quite different from those occurring *in vivo* Thus, one must be very cautious in attempting to relate the role of the altered enzyme reaction to a particular syndrome However as the complex interrelationships of diet and cellular enzymes are unraveled whole new fields will be opened for the treatment of clinical conditions by planned control of the diet

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Chapter 15

Dietary Interrelationships

By Robert A Harte, Bacon Chow and Barnett Sure

Introduction.—In the last edition of this book a comprehensive, critical review of relevant literature to 1953 included well over 200 references on the various facets of the problem of dietary interrelationships Perhaps the most striking impression received from evaluation of that literature is that hardly any study undertaken with any pair of nutrients has failed to show a significant interaction in terms of some nutritional or biochemical criterion This is not surprising, though, since each step of the chain of reactions through which a nutrient goes as it follows an appropriate metabolic pathway is mediated by at least one enzyme system, and the functioning of every enzyme system calls for the combined action of an apoenzyme (made up for the most part of amino acids) and a coenzyme (which usually includes a vitamin and/or a mineral element) However, the breadth of the experimental interrelationships brought out by these various studies underlines the statement that the recognition of the large number of them re-emphasizes the basic soundness of the principle of maintaining variety in foods in order to provide the most nutritious diet'[1]

Happily there has been, at least in this country, over the past few decades a steadily decreasing incidence of disease syndromes attributable to specific single nutrient deficiencies[2] Barring highly exceptional circumstances scurvy rickets, pellagra, and beriberi have virtually disappeared from the American scene[3] Indeed both the striking advances in food technology through which preservation of essential nutrients during food processing has been ever better achieved and the natural distribution of essential nutrients, where only very rarely is one found singularly in a food source emphasize the unlikelihood of significant increase in the incidence of single deficiency syndromes

The known nutrients, ignoring water and oxygen, may be divided into five large categories, the class to which any one is assigned depending upon its chemical structure and its physiologic function These categories are carbohydrates fats proteins, vitamins and minerals Each of them includes many individuals Not only have interrelationships been reported between members of a class but also between individual members of different classes and to some extent, between classes as a whole

In the following we will single out for attention what appear to be some of the more significant interrelationships The listing is necessarily not exhaustive because the number of possible interrelationships is extremely large Further the applicability of many of the experimental observations to human nutrition is by no means fully established

Calorie Interrelationships.—The calorie requirements of the vital processes are met by the energy released during the catabolism of combustible nutrients. The first three categories of nutrients, carbohydrates, fats and proteins, comprise the sources of energy in the dietary.[4] Within wide limits calories from any one of these sources may be regarded as completely replaceable by calories from any other of these sources. Limitations to this statement may be imposed by endogenous enzyme capacity, as well as by such factors as differences in the obligatory water demand, as they relate to the calorigenic source.

However, it must be borne in mind that the *utilization of carbohydrates, fats and proteins for energy is necessarily dependent upon the integrity of a variety of enzyme systems within the animal body*. These, in turn depend for their integrity and quantitative maintenance on exogenous supplies of vitamins, minerals and amino acids as well as upon the maintenance of sufficient water supply to insure the aqueous milieu in which the energy-releasing reactions are carried out. Hence it is apparent that even at this stage the biochemist, the nutritionist, the physiologist and the clinician must cope with complex problems of interdependence among the nutrients.

Protein-Energy Interrelationships.—In addition to being a source of energy, proteins (and perhaps more importantly their constituent amino acids) enjoy certain highly specific metabolic functions. Experimental studies in both animals and man going back to the early years of the century, and before, amply affirm through the application of many criteria that the utilization of ingested amino acids for their specific non calorigenic functions is markedly affected by the total caloric content of the diet and by the ratio of protein to non-protein calories.[5] Whether one studies growth (as measured by total weight gain or increase in body nitrogen), protein regeneration, or nitrogen balance substantially the same picture emerges. At a given total protein intake the utilization of the dietary nitrogen for non-calorigenic purposes first increases and then plateaus as the total energy intake increases.[6] In this experimental situation the value of the protein calorie-total calorie ratio at which the plateau effect begins is dependent in part upon the quality of the protein and in part upon the level of total protein intake selected for study.[7]

If, on the other hand, the experimental situation is modified so that the total caloric intake is kept constant, but the ratio of protein calories to total calories is varied, then the utilization of dietary protein for non calorigenic functions first increases then, passing through a maximum, decreases as the ratio is increased.[8] Here again the level of dietary protein corresponding to maximum utilization is dependent upon the quality of the protein, being in general higher for poorer quality proteins.

Amino Acid Interrelationships.—Some twenty odd naturally occurring amino acids have been identified as constituents of dietary proteins. Of these, eight have been described as essential in human nutrition, where the word *essential* has had conferred upon it the specific meaning "must be supplied exogenously." Despite the fact that a unique and specific need exists for each essential amino acid there is some evidence of inter

actions between some of them, as, for example leucine isoleucine and valine[9]

Further, there do exist certain very close chemical relationships between certain non essential and essential amino acids, e g, tyrosine and phenylalanine which differ only by a single hydroxyl group A number of experiments have clearly established that while adequate physiologic function is impossible when any one of the essentail amino acids is completely absent, there exist certain combinations where the presence of an abundance of a non essential amino acid significantly lowers the minimum level at which a particular essential amino acid must be present This generalization is amply documented for the phenylalanine-sparing effect of tyrosine[10] and for the methionine-sparing effect of cystine[11, 12, 13] In contrast, it has been shown, at least in animals that an abundance of hydroxylysine does not significantly affect the requirement for lysine[14] even though in this instance like in the phenylalanine-tyrosine relationship, the chemical difference is only a single hydroxyl group

The toxic effects of excesses of some of the amino acids both essential and non essential have been noted by many investigators[15–18] Some interesting interrelationships have been suggested by these studies, such as the ability of additional dietary arginine and glycine to counteract under certain conditions the toxicity of excess methionine[19] It has been suggested[20, 21] that such imbalances or toxicities may find therapeutic use in the treatment of virus or neoplastic disease

Amino Acid-Vitamin Interrelationships —There are a number of fairly specific amino acid-vitamin interrelationships where the metabolic roles of a given amino acid and a given vitamin overlap in all or part so that there exist reciprocal sparing of requirement for either in the presence of the other As typical of such situations the following may be cited

One of the important roles of the essential amino acid methionine is in transmethylation reactions where the amino acid functions as a methyl donor Under closely related circumstances not only methionine but both choline and Vitamin B_{12} may serve as methyl donors To a significant extent these nutrients may therefore spare each other so that an abundance of one will reduce (but not obviate) the requirement for another[22–28]

A second important interrelationship is represented by the sparing effect of tryptophan on niacin[9] The essential amino acid tryptophan serves as a precursor to niacin in certain living systems and an ample amount of dietary tryptophan will effectively prevent the development of the symptoms of pellagra which is commonly regarded as a niacin deficiency disease

As other examples of vitamin amino acid interrelationships a large dietary excess of glycine has been reported to increase the requirements for folic acid[30, 31] a lack of the vitamin results in defective metabolism of histidine[32–34]

Vitamin Interrelationships —There are perhaps some dozen or fifteen known vitamins of importance in human nutrition Perhaps because of the comparative simplicity with which experimental diets can be constructed with controlled amounts of one or another of these essential nutrients but probably as much because of the extensive penetrations made by following the roles of these substances in a host of fundamental meta

bolic processes, interrelations between them have been studied more extensively and in more detail than any other dietary interrelationships. In this section we shall attempt to highlight some of the more relevant findings for what appear to be the more important combinations which have been studied.

It cannot be emphasized too strongly, though, that translation of the experimental findings to other situations with other species must only be done with the utmost caution. For the most part the conclusions to which various experimenters have arrived came out of observations on highly synthetic systems. Little or nothing is known about the extent to which modification of the surrounding experimental situation would alter the result observed. For example, mention has already been made of the metabolic interrelationships between choline and methionine. In the light of that knowledge, any conclusions as to interrelationships between choline and Vitamin B_{12} can only be valid under dietary conditions controlled with respect to methionine.

The enormously complex interplay inherent in the multivariate system which is the human dietary enjoins on us the necessity to regard the experimentally derived interrelationships as little more than the crudest clues to what might be encountered in the uncontrolled situation. The usual experimental situation in which a vitamin deficiency state is studied involves the feeding of an otherwise adequate diet containing all the known nutrients except the one being tested. It is generally assumed, implicitly, that such a diet will create a deficiency only of the essential nutrient but there are important fallacies in this assumption. First, the administration of a diet deficient in a nutrient is very frequently followed by a marked reduction of food intake. As a result the intake of all of the other nutrients is reduced. Complete compensation for deficiencies resulting from lowered intake is impossible unless the experimenter resorts to forced feeding and the animals tolerate this heroic procedure. Second, in many instances the deficiency of a certain vitamin may adversely affect the absorption of one or more other vitamins, thus giving rise to secondary deficiencies. Third, an effect of a dietary deficiency in a single vitamin may be an increase in requirement for one or more other nutrients, so that relative secondary deficiencies may arise.

The problem is further complicated by the fact that, depending upon conditions, the interactions between two vitamins may be in the directions of either synergy or antagonism. Many of the observations on which our knowledge rests stem from studies of *in vitro* systems. Oftentimes, too, results from *in vivo* studies have been reported in conflict with the findings of others because of such uncontrolled variables as species, strain, over-all diet composition and even methodology. In many instances, too, reported findings only have validity in an experimental situation reflecting an overload of one or another of the nutrients under study to levels which are apt to be quite non-physiologic.

Out of a welter of evidence, not all of which is consistent, it may be concluded that animals fed diets deficient in thiamine, riboflavin, biotin or Vitamin B_6 excrete less niacin and its derivatives than animals fed otherwise complete diets.[35–40] Little or no effect was seen on the excretion of

niacin and its metabolites in the urines of animals fed diets deficient in pantothenate[41] or folic acid,[4] but the feeding of Vitamin B_{12} deficient diets is accompanied by reduction in the urinary excretion of N-1-methylnicotinamide[43] These findings, in general confirm the hypothesis that the conversion of tryptophan to niacin and the subsequent metabolic degradation of the latter is a complex chain of biochemical reactions the several steps of which are each mediated by one or more enzyme systems requiring various other vitamins for their coenzyme functions

Often vitamins have multiple metabolic functions and, therefore, two or more vitamins tend to overlap with respect to their roles in certain processes Perhaps an outstanding example of this is the major role apparently played in hematopoiesis by both folic acid and Vitamin B_{12}[44–46] There are close interrelations between these two vitamins and as their effects are evaluated with respect to different criteria results seemingly in conflict with each other are encountered For example the clinical manifestations of folic acid deficiency in human subjects have been reported as aggravated by the administration of small daily doses of Vitamin B_{1}[47,48] On the other hand, patients with megaloblastic anemia show a close correlation between the serum Vitamin B_{1} level and the urinary excretion of folic acid following administration of a parenteral loading dose of the latter[49] Each vitamin administered alone, is capable of eliciting a reticulocyte response in pernicious anemia patients in relapse but exacerbation of neurologic symptoms has been reported as a complication of therapy with folic acid alone[50] On the other hand, the neurologic disorders are commonly alleviated when adequate Vitamin B_{12} therapy is instituted[51]

In the forefront of current studies on vitamin interrelationships are investigations into the interrelationships between Vitamin B_{6} and Vitamin B_{1} Following oral administration of radioactive Vitamin B_{12} to adult or weanling male or female rats there is under otherwise comparable conditions less urinary excretion and less storage of radioactivity in specific organs (liver, kidneys gastrointestinal tract) in the animals maintained on Vitamin B_{6} deficient diets than on appropriate controls[5] Under the conditions of these experiments then it would appear that both the absorption and the storage of Vitamin B_{1} are reduced when the diet is deficient in Vitamin B_{6} the observed effects can be reversed if the deficient animals are subsequently injected with pyridoxine solution Similar experiments carried out with thiamine riboflavin and pantothenic acid failed to show any effect of these specific nutrient deficiencies on either absorption or deposition of vitamin B_{12} in selected organs

Studies which have been made to determine the manner in which the impairment of absorption of B_{12} by the Vitamin B_{6} deficient animal occurs have so far not fully clarified the problem In the presence of the deficiency, neither the stimulation of gastric secretion by histamine nor the addition of exogenous supplies of intrinsic factor improved the absorption of Vitamin B_{12} from the gastrointestinal tract[53] Since after thyroidectomy or in the presence of thyroid atrophy the absorption of orally administered Vitamin B_{12} is reduced[54] additional experiments were carried out to explore whether Vitamin B_{6} deficiency results in some endocrine disturbances which in turn affect the absorption of Vitamin B_{12} from the gastrointestinal

tract In Vitamin B_6 deficient animals no thyroid atrophy has been reported, but adrenal insufficiency has been observed

The absorption of orally administered Vitamin B_{12}, to groups of animals subject either to adrenalectomy, castration or splenectomy was compared with appropriate controls Reduction of absorption was seen in both the adrenalectomized and splenectomized groups It also was shown that adrenalectomized Vitamin B_6 deficient animals absorbed less Vitamin B_{12} than the non-adrenalectomized controls[53]

The role of the hypophyseal hormones in mediating adrenal function made it seem likely that if the adrenal function of the rat could affect the absorption of Vitamin B_{12} so too should hypophysectomy Accordingly, a series of studies were carried out to measure the absorption of Vitamin B_{12} by hypophysectomized animals to which, in various groups, replacement therapy was offered in the form of subcutaneous injections of ACTH or of TSH[53] Appropriate studies of the weights of the thyroids and adrenals showed that the samples of ACTH and TSH which were used in this study were relatively free of contamination with each other

The observed improvements in absorption of Vitamin B_{12} following administration of the hormones lead to the conclusion that both ACTH and TSH play roles in controlling its absorption The relative independence of these pathways suggests that at least two mechanisms influencing the absorption of Vitamin B_{12} from the gastrointestinal tract must exist[54]

Experimental impairment of adrenocortical function either directly by adrenalectomy, or indirectly by hypophysectomy, is followed by more or less marked decreases in the secretion of many hormones of adrenal origin In a partial attempt to pinpoint the specific adrenal hormone involved in Vitamin B_{12} absorption both Vitamin B_6 deficient and control animals were studied from the viewpoint of Vitamin B_{12} absorption in the presence of and in the absence of exogenous supplies of cortisone administered by injection The data obtained from such studies clearly suggest that the role of the adrenal glands on the absorption of Vitamin B_{12} may be primarily a cortisone effect, since an improvement in absorption by the Vitamin B_6 deficient animals is seen when the hormone is injected[55,56]

The livers of experimental animals deficient in Vitamin B_{12} contain not only more pantothenic acid but also more Coenzyme A activity than the livers of B_{12} fed controls[57–60] Conversely, an increase in liver B_{12} was reported in pantothenate deficient rats as compared with pantothenate fed animals[61] and dietary B_{12} has been reported to spare the requirements of the growing pig for pantothenate[6]

Ascorbic acid or thiamine *in vitro* at pH 7, reduce Vitamin B_{12} activity in microbial systems[63] On the other hand, under certain conditions ascorbic acid can replace in all or part, the Vitamin B_{12} requirement of some lactic acid bacteria[64]

Interrelationships among the fat soluble vitamins especially vitamins A, D, and E, have occupied the attention of researchers over a period of many years A wealth of information has accumulated bearing on the role of Vitamin E in influencing the storage of Vitamin A in the liver, and the rate of mobilization of such stores when Vitamin A deficient diets containing varying amount of Vitamin E are fed[65] It appears abundantly clear

that the liver stores of Vitamin A are increased to a greater extent with a given dose of Vitamin A when Vitamin E is co-administered, but when the exogenous supply of Vitamin A is large the significance of this effect diminishes

Administration of large doses of Vitamin A has been shown to decrease but not entirely eliminate the harmful effects of excess Vitamin D [66-69]

Thiamine deficiency is frequently accompanied by pronounced disturbance o riboflavin metabolism [70] which also often is seen in cases of panto thenic acid deficiency [71] partial protection from spontaneous seizures in experimental animals raised on pyridoxine deficient diets has been observed when the B_6 deficient diets were increased in their content of thiamine, riboflavin and pantothenic acid

The rat is known to differ significantly from the guinea pig and man in having a marked capacity to synthesize Vitamin C,[73] however, this synthetic capacity of the rat is considerably diminished in the face of thiamine[74] and riboflavin[75] deficiencies, so it may be inferred that these vitamins play a significant role in the biosynthesis of Vitamin C

Both thiamine and riboflavin avitaminoses are very common secondary dietary deficiencies both in human pellagra and in canine black tongue [76] Whether these observations, in fact, represent an interrelationship among these vitamins and niacin, or whether they simply reflect the fact that a niacin poor tryptophan poor diet such as would induce pellagra or black tongue, is commonly poor in thiamine and riboflavin would have to be elucidated, but the latter alternative is quite attractive in terms of current knowledge of the composition of food

Vitamin-Mineral Interrelationships —Since one of the major roles of many of the vitamins is to function as coenzymes in the host of intracellular enzyme systems responsible for overall metabolism and since, in so many instances too, the trace minerals play critical roles in enzyme systems, it follows that there must be literally hosts of interactions between the members of these two classes of nutrients These, however, are interactions occurring for the most part at the cellular level and are not likely to be encountered to any significant degree in persons ingesting customary foodstuffs

More serious, perhaps, are the chemical interactions between certain minerals and certain vitamins, the net effects of which are to destroy the vitamins before they can be ingested Thiamine is particularly sensitive to the action of minerals as they are found in certain salt mixtures [77] however, it would appear that the observed destruction is more likely a pH effect than the result of a specific chemical reaction between the vitamin and a particular cation [78]

Ascorbic acid, which plays an important role in the oxidation reduction mechanism of the body, reacts with certain cations,[79] notably iron, and may be subject to oxidative destruction before ingestion, if it is offered in a poorly formulated combination

Another type of vitamin mineral interaction is that seen in the roles of Vitamin E and selenium in liver necrosis in rats and in so-called exudative diathesis in chicks [80]

Mineral Interrelationships —Of considerable theoretical interest, although perhaps not of great practical importance, is the well documented role of copper in the incorporation of inorganic iron into hemoglobin [81] Less well known are the interactions between molybdenum and copper where these elements appear to exhibit reciprocal antagonism in certain species [8]

The existence of comparatively critical ranges of ratio for the optimal utilization of dietary calcium and phosphorus is well known[83] and, when the total amount of calcium and phosphorus fed is large, perosis has been induced in chicks as a result of a concomitant increase in the requirements for manganese [84]

The reciprocal intracellular relationship between sodium and potassium reflects itself in a markedly heightened toxicity of sodium in the presence of severe potassium depletion [85]

Miscellaneous Interrelationships —The effective utilization of calcium for bone formation during the growth of the young and during pregnancy requires optimal quantities of Vitamin D [86] In addition adequate circulating plasma protein levels are essential for efficient transport of calcium to the synthesizing sites [87]

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Chapter 16

Chemical and Other Additives to Foods

By Franklin C. Bing

Foods are commonly thought of as mixtures of protein, fat, carbohydrate, mineral elements and vitamins, and are so catalogued in tables of food composition. Other substances, though often disregarded, are also present in natural foods. Still other substances may be present in foods as eaten, having been introduced purposely or accidentally in small amounts; these substances are commonly referred to as food additives.

Without chemicals for use as pesticides, many foods could not be produced in the quantities needed today. Without chemical and other additives the methods of food processing, packing and distribution of today's food industry could not have been developed. The modern grocery store with its hundreds of items of nutritious foods—good tasting and of excellent keeping qualities, packaged in clean and convenient containers, and sold at economical prices—is a marvel of technological development to which the chemical and allied industries have contributed to a substantial extent.

Both industry scientists and public health workers have long recognized that the proper use of food additives requires not only the voluntary control of industry but also the rules that suitable laws and regulations could supply, and adequate administration of these rules by regulatory officials.

HISTORY OF LEGISLATION ON FOOD ADDITIVES

The earliest food laws, enacted when the problems of food additives were virtually non-existent, were directed against economic cheats, such as short weight, or against practices which were deceptive, such as the concealment of inferiority. Subsequent laws were made to safeguard the health of consumers by prohibiting the use of harmful or deleterious substances in or on foods. The burden of proof that a given substance was harmful or deleterious under such laws rested on the government.

The Federal law in the United States today requires a manufacturer to supply evidence of the utility and harmlessness of any proposed food additive before it may be used. The burden of proof thus rests on the person who desires to use an additive. This unique and desirable situation has come about only recently.

The basic food law in the United States is the Federal Food, Drug, and Cosmetic Act, which was passed in 1938. As a federal measure, of course, this Act, with its amendments, applies only to foods which are shipped in interstate commerce. Many of the states have their own food and drug laws so written that the federal law becomes state law too, with a minimum

of further action on the part of the state authorities From a practical point of view, the basic federal food law determines the rules and practices for the entire country

The developments which led to the present laws governing food additives began, in a sense, during World War II, when reports reached the general public of a remarkable new insecticide It had been produced in tonnage quantities and was used extensively during the war to control mosquitoes, and hence malaria, and to control other insect pests that can transmit human diseases Its use by the military had been of course, by troops trained in how to use it properly The late Dr H O Calvery of the Food and Drug Administration, and others, alerted by training and experience to the possibilities of harmful effects from this new insecticide, if improperly used, insisted upon testing its toxic properties before the product—soon familiar to all householders as DDT—was released for use by the civilian population This was in 1945 The awareneness of the scientists in the Food and Drug Administration, the United States Department of Agriculture, and the United States Public Health Service, in this instance represented an activity in the public interest beyond the requirements, perhaps even beyond the authority of the laws as then written It is fortunate that voluntary initiative worked so well, because the public, having no experience with its handling, and in reliance on wholly favorable and enthusiastic stories by writers who were themselves laymen, might easily have used the material carelessly and dangerously As it was, users were placed on guard, and to a large extent suitable precautions were exercised in handling the material, and DDT soon earned the reputation which it still enjoys of being a very valuable insecticide Numerous other new insecticides have since been introduced and have also gained wide acceptance

At the time, shortly after the conclusion of World War II, numerous substances were being offered to the food industry as intentional additives to foods Some of these intentional additives were nutrients and presented no unusual toxicological problems Others were introduced because of their preservative properties, or for their emulsifying properties, or because in some other functional way they aided in the processing of foods or favorably affected the characteristics of food products In some instances these substances had been introduced to the food industry without the benefit of suitable methods for their quantitative determination in foods, or in body tissues, which meant that their use could not be effectively controlled either by manufacturers or regulatory agencies, and the substances could not be studied thoroughly by investigators interested in the possible effects of the additives on the body

In 1949 the American Public Health Association recommended that the Federal Food, Drug and Cosmetic Act be amended to require pre testing, and approval before use of all food additives In 1950, Congress formed a House Committee to investigate the subject and, after extensive hearings, this Committee under the Chairmanship of Congressman James J Delaney, made reports recommending new legislation along similar lines In 1954, a bill to regulate residues of pesticides in foods was presented to the Congress by Dr A L Miller, who had been a member of the Delaney Commit

tee, this bill was adopted by both Houses and signed by the President Finally in 1958 the so-called Food Additives Amendment, which regulates food additives other than pesticides, was adopted The successful efforts to secure the enactment of these new sections of the law were made in large measure by university and industry scientists, by representatives of the important trade associations of the food and allied industries, and by representatives of individual manufacturers

PRESENT REQUIREMENTS

Pesticides —The term pesticide ' is a general one it includes insecticides, fungicides and other agents which are used to destroy organisms that are harmful to foods and crops Commercial pesticides must be registered with the United States Department of Agriculture, in accordance with the requirements of the Federal Insecticide Fungicide and Rodenticide Act of 1947 Each product must be shown to be useful for its intended purposes, and it must be labeled informatively with suitable directions for its use Under the Food Drug and Cosmetic Act residues of the pesticide must be shown to be harmless under the conditions of use or evidence in support of a tolerance must be submitted and approved A tolerance is the permissible maximum quantity of a pesticidal residue on fresh fruits and vegetables or other specified foods it is a quantity that is considered to be of negligible health significance Tolerances for fruits and vegetables apply only to residues of substances which result from their application prior to harvest

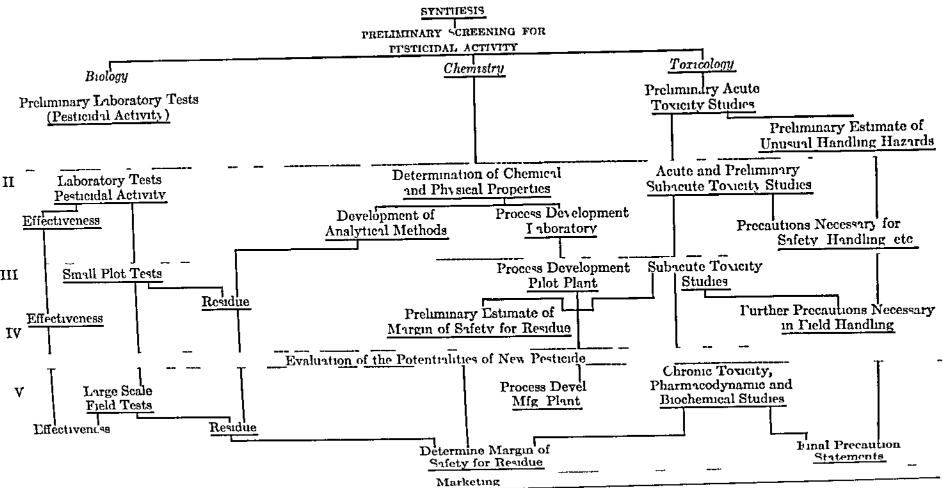
Among the frequently used pesticides today for which tolerances have been established are the following Aldrin Chlordane, DDT, Dieldrin EPN, Ferbam Heptachlor Lindane Methoxychlor Parathion TDE, Toxaphene Zineb and Ziram Each of these as well as other pesticides for which tolerances have been established has been thoroughly tested in accordance with the requirements of the law A useful book, incidentally, for physicians and others who may desire information about the chemical and toxicological nature of commercial pesticides and other preparations which may be involved in cases of chemical poisoning, is that of Gleason Gosselin and Hodge [1]

At the present time no residues of certain insecticides are permitted on fruits and vegetables, because of their degree of toxicity It is sometimes said that a zero tolerance has been established for these substances This means that no detectable quantity is permitted on a food, and any food product showing even a trace will be considered adulterated under the law

Some pesticides are exempt from the requirement of a tolerance for residues thereof The reason is that these substances are volatile and are quickly dispelled from foods to which they are applied

Valuable suggestions regarding toxicologic procedures and the interpretation of experimental data on pesticides and other food additives are presented in a series of essays by members of the staff of the Food and Drug Administration Except for articles such as these published by government scientists and a limited number of articles published by industry

TABLE 47.—CHART SHOWING STAGES IN THE DEVELOPMENT OF A NEW PESTICIDE
(From "Safe Use of Chemical Additives in Foods," Food Protection Committee, 1952)



scientists, there is little material available in the scientific literature that deals with experimental studies of chronic toxicity

In Table 47 there is reproduced a chart showing the stages in the commercial development of a new insecticide This chart appeared in a pamphlet prepared in 1952 by the Food and Nutrition Board s Food Protection Committee[3] The pamphlet is entitled 'Safe Use of Chemical Additives to Foods ' and the chart is of interest because it shows the elaborate procedure for testing which was being recommended even before the enactment of the Miller pesticide amendment, and which in general was being followed even then by industry The toxicity studies for many substances require tests to be made on two species of animals—one of which is not a rodent—for periods of as long as two years The amount of labor involved in the introduction of a new pesticide can thus be seen to be very appreciable On the whole the pesticide section of the Act has operated very well, and to the satisfaction of both industry and government

Additives Other Than Pesticides —In 1956 the National Research Council published a report of the Food Protection Committee entitled The Use of Chemical Additives in Food Processing [4] This booklet represented an attempt to list the substances which were known to be purposely added to foods In December 1958 the Food and Drug Administration published a listing of food additives which they considered to be safe for use[5] They pointed out that their lists were incomplete, that salt pepper sugar, vinegar baking powder and mono-sodium glutamate, for example are regarded as safe for their intended use, though these materials are not listed Tables 48 and 49 provide illustrative listings of food additives regarded as safe, when used in accordance with good manufacturing practices

TABLE 48 —FOOD AND DRUG ADMINISTRATION LIST OF SAFE ADDITIVES 1958
(When used according to good manufacturing practices)

BUFFERS AND NEUTRALIZING AGENTS

Acetic acid
Aluminum ammonium sulfate
Aluminum sodium sulfate
Aluminum potassium sulfate
Ammonium bicarbonate
Ammonium carbonate
Ammonium hydroxide
Ammonium phosphate (mono- and dibasic)
Calcium carbonate
Calcium chloride
Calcium citrate
Calcium gluconate
Calcium hydroxide
Calcium lactate
Calcium oxide
Calcium phosphate
Citric acid
Lactic acid
Linoleic acid
Magnesium carbonate
Magnesium oxide
Oleic acid
Potassium acid tartrate
Potassium bicarbonate
Potassium carbonate
Potassium citrate
Potassium hydroxide
Sodium acetate
Sodium acid pyrophosphate
Sodium aluminum phosphate
Sodium bicarbonate
Sodium carbonate
Sodium citrate
Sodium hydroxide
Sodium phosphate (mono- di , tri)
Sodium potassium tartrate
Sodium sesquicarbonate
Sulfuric acid
Tartaric acid

TABLE 48.—*Continued*

COLORS

Carmel
Carbon black
Charcoal
Titanium dioxide
Ultramarine blue

PRESERVATIVES

Sequestrants

Calcium acetate
Calcium chloride
Calcium citrate
Calcium diacetate
Calcium gluconate
Calcium hexametaphosphate
Calcium phytate
Citric acid
Dipotassium phosphate
Disodium phosphate
Monocalcium acid phosphate
Monoisopropyl citrate
Potassium citrate
Sodium acid phosphate
Sodium citrate
Sodium diacetate
Sodium gluconate
Sodium hexametaphosphate
Sodium metaphosphate
Sodium phosphate (mono-, di-, tribasic.)
Sodium potassium tartrate
Sodium pyrophosphate
Sodium tartrate
Sodium tetrapyrophosphate
Sodium tripolyphosphate
Tartaric acid

Antimycotics

Calcium propionate
Potassium sorbate
Propionic acid
Sodium propionate
Sodium sorbate
Sorbic acid

Antioxidants

Ascorbic acid
Ascorbyl palmitate
Calcium ascorbate
Erythorbic acid
Sodium ascorbate
Tocopherols

General

Acetic acid
Citric acid
Phosphoric acid
Sorbitol

MISCELLANEOUS

Aluminum sodium sulfate
Aluminum sulfate
Butane
Calcium phosphate, tribasic
Carbon dioxide
Carnauba wax
Glycerin
Glycerol monostearate
Helium
Magnesium carbonate
Magnesium hydroxide
Monoammonium glutamate
Nitrogen
Papain
Propane
Propylene glycol
Triacetin (Glyceryl triacetate)
Tricalcium phosphate
Sodium carbonate
Sodium phosphate
Sodium polyphosphate

NON NUTRITIVE SWEETENERS

Calcium cyclohexyl sulfamate
Calcium saccharin
Saccharin
Sodium cyclohexyl sulfamate
Sodium saccharin

TABLE 48—*Continued*

NUTRIENTS

Ascorbic acid	Potassium chloride
Calcium carbonate	Pyridoxine hydrochloride
Calcium oxide	Riboflavin
Calcium pantothenate	Riboflavin 5-phosphate
Calcium phosphate (mono, di tribasic)	Sodium pantothenate
Calcium sulfate	Sodium phosphate (mono-, di, tribasic)
Carotene	Thiamine hydrochloride
Ferric phosphate	Thiamine mononitrate
Ferric pyrophosphate	Tocopherols
Ferric sodium pyrophosphate	α tocopherol acetate
Ferrous sulfate	Vitamin A
Iron, reduced	Vitamin A acetate
1—lysine monohydrochloride	Vitamin A palmitate
Niacin	Vitamin B_{12}
Niacinamide	Vitamin D_2
2—Pantothenyl alcohol	Vitamin D_3

STABILIZERS

Agar agar	Carragheen
Carob bean	Guar gum

EMULSIFYING AGENTS

Acetyl tartaric acid esters of mono- and diglycerides except lauric	Monosodium phosphate derivates of mono- and diglycerides except lauric
Mono- and diglycerides except lauric	Propylene glycol

TABLE 49—FOOD AND DRUG ADMINISTRATION LIST OF TOLERANCES FOR FOOD ADDITIVES, 1958

MISCELLANEOUS

Aluminum calcium silicate	2%	Table salt
Calcium silicate	5%	As an anticaking agent in baking powder
Calcium silicate	2%	As an anticaking agent in table salt
Caffeine	⅛ to ¼ grain in 6-oz bottles of cola drinks	In cola drinks
Ethyl formate	15 parts per million	When used as fumigant for cashew nuts
Magnesium silicate	2%	Table salt anticaking agent
Ox Bile Extract U.S.P. (solids)	0.01%	Egg whites
Taurocholic acid (or its sodium salt)	0.01%	"
Tricalcium silicate	2%	As an anticaking agent in table salt
Triethyl citrate	0.25%	Egg whites

TABLE 49.—*Continued*

	NUTRIENTS	
Copper gluconate	0.005%	In any food
Cuprous iodide	0.01%	Used in table salt as source of dietary iodine
Potassium iodide	0.01%	" " "
	PRESERVATIVES	
	Antimycotics	
Caprylic acid	—	Antimycotic in cheese wraps
Potassium bisulfite	—	Not in meats or in foods recognizable as a source of vitamin B_1
Potassium metabisulfite	—	" " " "
Sodium benzoate	0.1%	No special use specified
Sodium bisulfite	—	Not in meats or in foods recognizable as a source of vitamin B_1
Sodium metabisulfite	—	" " " "
Sodium sulfite	—	" " " "
	Antioxidants	
Benzoic acid	0.1%	No special use specified
Butylated hydroxytoluene	0.02%	Edible fats and oils
Butylated hyroxyanisole	0.02%	" " "
Dilauryl thiodipropionate	0.02%	" " " "
Gum guaiac	0.1%	" " "
Nordihydroguaiaretic acid	0.02%	" " "
Propyl gallate	0.02%	" " " "
Thiodipropionic acid	0.02%	" " " "
	General	
Sulfur dioxide	—	Not in meats or in foods recognizable as a source of vitamin B_1
	Sequestrants	
Isopropyl citrate	0.02%	No special use specified
Sodium thiosulfate	0.1%	Salt
Stearyl citrate	0.15%	No special use specified
	STABILIZERS	
Magnesium stearate	—	As migratory substance use in manufacturing plastic film in wrapping foods
	SURFACTANTS	
Cholic acid	0.01%	Egg white
Desoxycholic acid	0.01%	" "
Glycocholic acid	0.01%	" "

The number of calcium salts is worthy of comment The extent of the usage of these functional chemicals by the food industry is sufficient, it has been calculated to supply about one-fifth of the dietary calcium requirements of the people in the United States This is more than any single group of foods contributes, with the exception of milk and milk products

No flavoring materials are included in these lists these will be the subject of a future report Coal-tar colors are not listed, because they are subject to the provisions of another section of the law

In January 1959, however the Secretary of Health, Education, and Welfare stated that the consumer "is not receiving adequate protection against the use of colors in food drugs and cosmetics" At least three outbreaks of illness traceable to the consumption of foods containing excessive quantities of permitted dyes have occurred One of these involved nearly 200 persons, mostly children who had consumed popcorn colored with a dye that by modern testing methods has been shown to be not safe for use in human foods This dye and several others that have not passed modern tests have been banned for further use in foods But it is estimated that it would take the laboratories of the Food and Drug Administration with existing facilities, about 20 years to complete all of the testing that needs to be done on coal tar colors now in use The Department, the statement goes on to state, is prepared "to support legislation to put it in a position where it can provide the consumer with better protection than is the case today "[8]

The suggestion has been made that if coloring matters for use in foods were made subject to the same requirements as now pertain to other food additives the problem of controlling the use of food colors would be greatly simplified

Chemicals used in meat packing plants which operate under the Federal Meat Inspection Act administered by the Department of Agriculture have long had to be approved before they were allowed on the premises of a plant The Department of Agriculture also administers the Poultry Products Inspection Act The substances, which may become additives of food products, that are subject to these laws are reviewed by the Food and Drug Administration as a service to the Department of Agriculture Among the chemicals permitted on poultry is chlorotetracycline the tolerance is 7 p p m This antibiotic serves a valuable function as a preservative Evidence shows that cooking destroys all of the chlorotetracycline that may be present

The use of antibiotics and of hormones such as diethylstilbestrol in the feeding of farm animals comes under the jurisdiction of the Food and Drug Administration

In general, the requirement is that potent drugs which are administered to farm animals to promote growth or feed utilization or both must not be detectable in significant quantities in the tissues eggs, or milk or any other edible product

CONCLUSIONS

Someone has observed that is is almost impossible to discuss food additives without running the risk of conveying the wrong impression Such

was certainly the case during the several years that the desirability of suitable laws to require pre-testing of food additives was being thoroughly explored by interested groups Now that in the United States these laws have been enacted, it may be anticipated that the tenor of articles directed to the general public will be more moderate and factual Food additives should be viewed as a distinct contribution of science to the food industry and to the public The control exercised over their use in the United States is being studied by other countries where food additives and their relation to health are under active consideration

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Chapter 17

Laboratory Aids in the Diagnosis of Malnutrition

A Biochemical

By R F Krause

INTRODUCTION

In considering a fully developed state of malnutrition it is convenient to classify the sequence of events as (1) inadequate ingestion (2) decreased bodily reserves (3) impaired function and (4) anatomical lesions[1] Bodily reserves are commonly determined by chemical assessment of tissues, blood and urine Laboratory tests have long been used as aids in the diagnosis of fully developed states of malnutrition and in following therapeutic responses Such tests have been used only recently to detect early or incipient stages of malnutrition where the general health of the individual is impaired without showing signs of physical change The aim of this chapter is to record some of the laboratory tests most widely used in evaluating malnutrition and to discuss their reliability and fitness for diagnosing deficiency states It is of course, impossible to include all the laboratory methods which have been used

In selecting an appropriate laboratory method for studying a nutritional problem it is necessary to have clearly in mind the objectives of the investigation In general these objectives fall into three categories, namely clinical diagnosis, fundamental research and nutritional survey work In most instances workers in the first two areas desire more accurate methods and can tolerate more intricate procedures than can those interested in a survey The latter investigators are mainly concerned with such considerations as cost, simplicity of technique, speed etc Regardless of the purpose, laboratory findings are to be interpreted in relation to other evidence such as the history and physical findings

COMMON LABORATORY TESTS IN UNDERNUTRITION

The simple routine analysis of blood and urine will aid in evaluating the nutritional status of the patient A discussion of serum protein and hemoglobin levels in undernutrition is given under separate headings The blood sugar level is found to decrease during the early period of fasting only to return to pre fasting levels after a week or two Wollenberger and Linton[2] reported that fasting produces a marked impairment in the glucose tolerance test This fact should be considered when evaluating the glucose tolerance curve Blood cholesterol levels also decrease during starvation

The blood urea increases during the first week of fasting and later returns to pre-fasting levels. The urea levels parallel quite closely the changes in non-protein nitrogen (NPN) concentrations.[2] The only NPN constituent of blood that shows a consistent increase during fasting is the uric acid fraction. Keys reported that there is a decrease in blood uric acid content during semi-starvation.

Practically every observer of starving conditions has reported polyuria and nocturia. The urine of the semi-starved person is classically a pale fluid of no pigment, very little sediment, low specific gravity, and no albumin. Since protein intake sets the range for urinary nitrogen excretion, it is not surprising that there is a decreased excretion during starvation, providing, of course, the starvation diet is low in protein. Uric acid, amino-nitrogen, and NH_3 excretion is elevated during fasting while creatinine is decreased. Ketone bodies are commonly found in the urine of fasting individuals. Keys[4] reported, in his studies on semi-starvation, that there was an absence of ketosis in spite of a weight loss of 24 per cent of the original weight. Ketosis also does not seem to develop during periods of weight reduction in obese individuals. The calcium content of urine is usually low during semi-starvation.

HEMOGLOBIN AND IRON DEFICIENCIES

A reduction in the concentration of oxygen-carrying substance (hemoglobin) in a certain volume of blood is clinically termed anemia. The diagnosis of various types of anemia has been discussed in Chapter 10A. Among the substances concerned in erythropoiesis are iron, cobalt, copper, protein and various vitamins, especially vitamin C and the B vitamins. In view of the many materials known to be necessary for the production of red blood cells, it is not surprising that the level of hemoglobin has been widely used in evaluating nutritive state.

Methods.—The fact that there are many methods for the determination of hemoglobin implies that none are ideal. The *direct color comparison* made by diluting blood with water has the disadvantage that shades of red are difficult to match colorimetrically. However, if a photoelectric instrument is used, the color of the solution is no disadvantage. Diluting the blood with ammonia has become popular, because the color of the oxyhemoglobin formed with ammonia is stable. The *acid hematin* methods are widely used for hemoglobinometry, because the brown color is more easily matched than the red color of the "direct method." Several disadvantages of the acid hematin method must be recognized:[5] (1) The color of acid hematin does not reach its maximum intensity until the end of one hour, however, after ten minutes 95 per cent of the final color has been developed. (2) No truly satisfactory standard has been devised and non-hemoglobin substances interfere. (3) The personal equation introduces errors when the visual methods are used. This criticism is now met in part by the use of photoelectric colorimeters. The *alkaline hematin* method has the advantage over the above methods in that all active and inactive forms of hemoglobin, such as carboxyhemoglobin, methemoglobin, and sulfhemoglobin, are converted to hematin which is the sub

stance determined Then, too, an alkaline solution gives a better dispersion of proteins and fats in blood Bessey and Lowry[6] have designed a satisfactory micromethod for the alkaline hematin determination of hemoglobin which has been used in nutritional survey work The *cyan hematin* method has a high degree of accuracy and has the theoretical advantage that, in the hemin standard, the hemin is used in the theoretical proportion of four molecules of hemin to one of hemoglobin

Specific gravity methods have been used for calculating hemoglobin[7] Although the major premise that the corpuscular hemoglobin concentration is constant is incorrect, the method is useful in survey studies It is claimed to have an accuracy of ± 2 per cent

Regardless of the method used it is essential that it be standardized against one of the following four methods[8] (1) iron content method[9,10] or the titanous chloride procedure of King *et al*,[11] (2) *oxygen capacity procedure*,[12] (3) method of Rimington[13] using the pyridine hemochromogen complex, and (4) the crystalline hemin method of Horecker[14] It is common practice to express hemoglobin values in per cent This is unfortunate since it is obvious that there are normal variations in hemoglobin values in the same person as well as for different ages sexes and geographical localities To be accurate, therefore one should set up normal values for each sex and for children of different age groups

The counting chamber is commonly used to determine the erythrocyte count even though there is a recognized error of about 8 per cent Blum[15] has proposed a photoelectric method for determining the red cell count It is possible that such a procedure may be practical for the erythrocyte count in survey work

Applications —Wintrobe[5] has proposed a generally accepted standard set of normal values for red blood corpuscles for various ages and sexes He gives as a normal hemoglobin concentration in this country for adult males 16 0 ± 2 gm per 100 ml of blood and for females 14 0 ± 2 gm per 100 ml , the red cell count for adult males 5 4 ± 0 8 million/mm ^{3}, for females 4 8 ± 0 6 million/mm ^{3} and for both females and males a mean corpuscular volume of 87 ± 5cμ and a mean corpuscular hemoglobin concentration of 34 ± 2 per cent

If one knows the red blood cell count the volume of packed erythrocytes, and the hemoglobin concentration, it is then possible to calculate the mean corpuscular volume and mean hemoglobin concentration From these data one can arrive at a morphological classification of the anemia In an iron deficiency anemia for example, the mean corpuscular hemoglobin concentration is less than 30 per cent and the mean corpuscular volume generally is less than 80 cμ The anemias due to a deficiency of anti anemic principle as seen in sprue and pernicious anemia, are classified as having a mean corpuscular volume greater than 94 cμ and a mean corpuscular hemoglobin concentration greater than 30 per cent

The hypochromic microcytic (iron deficiency) anemia is probably one of the most frequent types of anemia met in clinical practice In addition to changes in cell morphology it is characterized by low serum iron Low serum iron may also develop as the result of an infection[16]

Until a few years ago iron deficiency states had not been well investigated

due in a large part to old macro-methods which required 1 to 10 ml of blood and, in addition, were time consuming Bessey[17] has described a micro-method that requires 20 cmm of serum He has stated that values below 60 micrograms per cent are indicative of an iron deficiency state A diurnal variation in the plasma iron levels has been reported[18] Normal serum iron varies from 60 to 150 micrograms per 100 cc[19] Frequently, the unsaturated iron-binding capacity of the serum is also determined[20] This procedure may be helpful in distinguishing between the anemia of infection and the anemia of iron deficiency since in the latter condition the iron-binding capacity is increased Recent investigations using isotopic Fe^{59} have indicated that the rate of turnover of this iron furnished a reliable index of erythrocyte formation[21] Radioactive iron has also been used in a mass study of nutritional status of school children[22]

It is generally accepted that the concentration of hemoglobin is one of the indices to be used in appraising the nutritional status of a single individual or of a group of individuals It is necessary, however, to bear in mind the limitations of the methods used and the normal variations commonly encountered It must also be remembered that the hemoglobin level is the resultant of a series of bodily processes, and that a break in the chain of synthesis or an added stress to the hematopoietic mechanism may result in a deficiency state from which there may result many diversified bodily manifestations

SERUM PROTEIN DEFICIENCY

Methods — The measurement of the total serum protein concentration and the ratio of the various serum protein fractions are commonly used as aids in assessing nutritional status The macro- or micro-Kjeldahl procedures were first used in determining the serum protein level These methods, though cumbersome, are very reliable and should be used where accurate determinations are desired In order to facilitate speed and simplicity, specific gravity methods have been designed and used The copper sulfate method of Phillips Van Slyke *et al*,[3] the falling drop method of Barbour and Hamilton,[4] and the micro-method of Lowry and Hunter[5] are some examples of the specific gravity methods in use today The accuracy of these methods for determining serum protein has been questioned[6] Looney[7] has stated that the specific gravity of blood serum is not a simple function of the concentration of protein, and that the degree of error in calculating the protein value from the specific gravity in any one individual may be large This error he has attributed to such blood constituents as salts and serum lipids Lowry and Hunter have considered such possible sources of error and have demonstrated that it would be necessary to double the normal concentration of serum lipids, blood glucose, or nonprotein nitrogen in blood in order to influence the serum protein level by 0 1 gm per cent They feel that it would be an extremely rare condition where any of these factors would seriously affect calculating serum protein levels from serum specific gravity measurements They likewise found little variation between their gradient tube method and the Kjeldahl method on a series of patients with various states of pathology excluding liver disease

Atchley[28] found good agreement between the various specific gravity and Kjeldahl methods.

The fractionation of the various components of serum proteins is commonly carried out by the salt precipitation method of Howe.[29] It is now recognized that the serum "albumin" values are too high, partly because alpha 1 and alpha 2 along with beta globulin are included in the albumin determination. Another method for serum protein fractionation is the alcoholic precipitation technique.[30] Probably the most accurate method of fractionation is by electrophoresis. This method is based on the principle that the various protein fractions of serum have a specific mobility in an electric field. Paper chromatography also has been used in separating serum proteins.[31,32] Recently there has been described a micro-electrophoretic separation of serum proteins using a drop of blood.[33] Jager *et al*[34] have compared the electrophoresis method and the various chemical estimations of human serum albumin and have found the saturated magnesium sulfate method to give the best numerical agreement with electrophoretic values. In their hands, the methanol method was less satisfactory than the salting out procedure. For clinical purposes either the salting out procedure or the alcoholic precipitation method is satisfactory, providing their limitations are recognized.

Applications.—The normal range for total serum protein in adults is between 6 to 8 gm per 100 ml serum; for serum albumin 4.0 to 5.5 gm per 100 ml. The serum protein level in children is reported to be at its lowest level at around four weeks of age averaging 5.3 gm per cent and then progressively increasing until adult values are attained at the age of four years.[35]

According to the concepts proposed by Whipple[36] and Schoenheimer,[37] the proteins of the body exist in dynamic equilibrium with plasma proteins. Various workers have used this thesis to justify the use of serum protein levels as a means of evaluating protein nutrition. The accuracy, however, of using the serum protein levels as an index of protein status in the body has been questioned on the grounds that the level of protein in the blood does not always accurately reflect the concentration of protein in the tissues. Keys[4] has stated that The plasma protein level, as such is of dubious merit in evaluating a person's nutritional status at least in so far as it pertains to the protein stores in the body. A low plasma protein level, especially one in which the decrease is due primarily to change in the albumin fraction may indicate that the person has suffered from a dietary protein deficiency or insufficient caloric intake. There are however many normal persons in good nutritional status who have levels comparable to those exhibited by semi starved persons. Karel Wilder and Beber[38] have endeavored to evaluate protein nutrition in the aged by electrophoretic examination of serum proteins in young and old men. They observed a decrease in total protein and albumin and elevations in all globulin components of old men. It is suggested by Watkins *et al*[39] that this difference may be explained on the basis of inadequate dietary protein in the aged.

The presence of hypoproteinemia is generally considered positive evidence of severe tissue depletion. Sachar *et al*[40] have calculated that

Applications —There have been numerous suggestions as to the normal range for vitamin A and carotene in the blood Goldsmith[69] has reported that the normal values for carotene range between 50 to 400 micrograms per 100 ml of serum and for vitamin A 30 to 70 micrograms per 100 ml of serum Bessey[70] has classified blood levels in terms of poor, fair, good, and excellent The poor range begins with 19 μg per cent for vitamin A and 74 μg per cent for carotene The excellent range starts with 50 μg per cent and 200 μg per cent for vitamin A and carotene respectively The teams of Krause and Pierce[71] and Szymanski and Longwell[72] both found average plasma vitamin A and carotene levels in normal children to be about 38 μg per cent and 116 μg per cent respectively Kagan[73] in a study on the vitamin A levels in infants and children, reported the average fasting level under six months of age to be 24 μg per cent, 32 μg per cent in the group six months to one year, and 38 μg per cent in children over one year A significant seasonal variation has been reported for carotene but not for vitamin A Merrow, Krause *et al*,[74] in a study of nutrient intake and serum levels, noted that nutrient intake of vitamin A and carotene reflected serum levels of vitamin A and carotene respectively The serum level of carotene reflected the nutrient intake of carotene, but the serum level of vitamin A did not reflect the nutrient intake of vitamin A There appears to be no significant difference between fasting and random sampling of blood on the vitamin A level, providing there has not been ingested any form of vitamin A concentrate

Following a single ingestion of vitamin A in oil or in aqueous dispersion the level of vitamin A in the blood rises to a maximum in about three hours for the latter and five hours for the former menstrum, and in both cases returns to normal in approximately twenty-four hours[71,73] The magnitude of the response to the test dose is greater with vitamin A dispersed in aqueous media

The relationship between serum levels and liver stores has been examined by Popper *et al*[75] using the fluorescence microscopy method They found good correlation between liver stores and serum levels of this vitamin Krause[76] using chemical methods, found that an inverse relationship existed between blood and liver levels of vitamin A in normal rats Blood levels of vitamin A and carotene have been called an expression of liver function

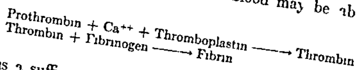
Popper *et al*[77] have expressed the belief that the vitamin A alcohol level of the blood is a better index of hepatic storage and vitamin A nutrition than is the total vitamin A level The latter is influenced by a postprandial rise, whereas the alcohol level is not In the fasting state 80 per cent of the vitamin A circulates in the blood as the alcohol form The elevation of blood vitamin A in the postprandial state is due largely to an increase in the ester form The ester variety disappears in about twenty four hours after the ingestion of the vitamin The separation of the ester and alcohol form is carried out best by the chromatographic absorption method[78]

It has been shown repeatedly that when human subjects partake of diets low in carotenoids and vitamin A with the remaining nutrients adequate, a significant increase in the rod threshold of the dark-adapted eye occurs

after a somewhat varied period of time.[79] At present there is considerable controversy regarding the correlation between this functional method of assessing adequate vitamin A nutrition and plasma levels of this vitamin.[69] There is little doubt that in vitamin A deficiency states there is a prolonged dark adaptation period. However, one must appreciate that a number of other factors contribute to individual variation; among these may be included the genetic factor, previous night vision training and previous exposure of the eyes to high intensities of light.

VITAMIN K DEFICIENCY

The prominent sign of vitamin K deficiency is an increase in the time required for the blood to clot. The clinical manifestation is hemorrhage. The reactions involved in the clotting of blood may be abbreviated as follows:



$$\text{Prothrombin} + Ca^{++} + \text{Thromboplastin} \longrightarrow \text{Thrombin}$$
$$\text{Thrombin} + \text{Fibrinogen} \longrightarrow \text{Fibrin}$$

If there is a sufficient reduction in the concentration of any of these reacting substances in the blood, there is a prolongation of the time required for the blood to clot. The hemorrhage that occurs in vitamin K deficiency is due not only to a lack of prothrombin and proconvertin, but also plasma thromboplastin component (PTC).[80] Methods designed for the determination of menadione (2-methyl-1,4-naphthoquinone; vitamin K) involve the reduction of the menadione-protein complex of blood with stannous chloride[81] and chromatography which separates this quinone from other quinones.[82] Such procedures are not practical to determine vitamin K deficiency since administered vitamin K quickly disappears from the blood.

In general, prothrombin is measured by its ability to form thrombin which in turn reacts with fibrinogen to form a clot. Actually, in most cases prothrombin activity, not its concentration, is measured. Brambel[83] has published an excellent discussion of the various methods used. For clinical purposes, the plasma prothrombin time of Quick with various modifications has been used widely.[84] The so-called bedside method[85] is reported to be of considerable value for the general practitioner. This test is carried out by drawing fresh blood and placing it in a tube containing a measured amount of thromboplastin. A clot normally should form in twenty-five to forty seconds. In general, if the prothrombin clotting time is not greater than 20 to 25 per cent above normal, bleeding does not occur on the basis of prothrombin deficiency.

In view of the number of variable factors other than prothrombin content that influence the prothrombin time plus the variety of methods used in determining it, it is not surprising that it is difficult to define a prothrombin concentration below which hemorrhage will occur. By the method of Rosenfield and Tuft,[86] a prothrombin concentration between 5 to 10 per cent of normal is a safe range.[87] It has been said, "The information afforded by the measurement of prothrombin in the circulating blood

is much more nearly accurate in the prediction of the tendency of a patient to bleed than is the measurement of the coagulation or bleeding time as formerly used in the consideration of such a tendency "[88] The failure of hypoprothrombinemia to respond to vitamin K can be a valuable liver function test

VITAMIN D DEFICIENCY

In determining the state of nutrition with respects to vitamin D, one has to rely on such indirect methods as blood levels of calcium, inorganic phosphate, and alkaline phosphatase No satisfactory chemical methods are available to measure either the concentration of this vitamin, its provitamin or a metabolic product

In rickets there is generally a decreased blood level of inorganic phosphorus and an associated rise in alkaline phosphatase activity Alteration of serum calcium is not so consistent, but there is generally a low level These changes are, however, not specific for vitamin D deficiency In uncomplicated cases of hyperactivity of the parathyroid, there is generally an elevated serum calcium associated with a decreased level of serum phosphate The alkaline phosphatase is increased above normal in various conditions other than rickets, such as hyperparathyroidism, Paget's disease osteomalacia, and metastatic carcinoma

Methods —With the advent of the micromethod of Bessey *et al*,[89] the use of alkaline phosphatase as a means of evaluating the state of vitamin D nutrition has become popular, especially in survey studies This method requires only 5 to 20 cmm of serum The reagent, sodium p-nitrophenyl phosphate, is a colorless compound but with the splitting off of the phosphate group the chromogenic salt of p-nitrophenol is liberated The product of the phosphatase reaction on the reagent serves directly as a measure of enzymatic activity One p-nitrophenyl phosphate unit is equivalent to 1 8 Bodansky units or one King-Armstrong unit is equivalent to 7 3 units of p-nitrophenyl phosphate The normal level of serum alkaline phosphatase is given as 1 5 to 4 0 Bodansky units for the adult and 5 to 14 units for the child

Most of the procedures for the determination of inorganic phosphorus in blood or serum are modifications of the method of Bell and Doisy[90] According to this method, the protein free serum or blood is treated with molybdate in acid solution, which forms phosphomolybdate The latter is reduced by the excess molybdate to give a blue color Normal serum inorganic phosphorus levels range between 3 to 4 5 mg per cent for adults and 4 to 6 mg per cent for children

The methodology and normal range for serum calcium have been presented earlier in this chapter An empirical rule for determining if a child is rachitic is to calculate the product of the serum phosphorus and serum calcium If it is below 30 rickets is present or will develop but not if it is above 40

VITAMIN E DEFICIENCY

There are comparatively few chemical methods for the determination of tocopherols in blood Emmerie and Engel[91] have developed a method

based on the reduction of ferric to ferrus iron by tocopherols The amount of reduced iron is then determined as an a-a'-dipyridyl complex Quaife and Harris[9] have simplified this procedure and obviated the interference of such compounds as carotene and vitamin A Nair and Magar[93] have developed a rapid clinical method for determination of tocopherol which involves the addition of phosphomolybdic acid in glacial acetic acid to a non saponifiable extract of serum and measuring the color intensity spectrophotometrically The average plasma levels range between 0 5 to 1 5 mg per 100 ml[94] Low levels are seen in new-borns and in patients with intestinal absorption defects steatorrhea, and liver disease Low serum tocopherol levels are frequently associated with creatinuria and in infants with cystic fibrosis of the pancreas and biliary atresia There has also been observed a decreased resistance to peroxide hemolysis[95 96] High values occur in normal pregnancy in some diabetics, and in various diseases associated with an elevation of the blood cholesterol

THE USE OF URINARY EXCRETION STUDIES IN VITAMIN DEFICIENCIES

The determination of the urinary excretion level of a vitamin or its metabolites has been widely used for evaluating the nutritive state For obtaining urinary samples various methods have been used such as (1) random postprandial (2) fasting samples (3) twenty-four hour urine samples and (4) urine samples following saturation loading or tolerance testing The question as to which method gives the most accurate picture of the nutrient state is a debatable one

Johnson and associates[97] studied urinary excretion of chlorides, ascorbic acid, thiamine N-methylnicotinamide and riboflavin on a group of soldiers living on field rations They came to the following conclusions (1) fasting samples were preferable to load tests (2) random urine samples were to be avoided and (3) the rate of excretion in the morning before breakfast was a more reliable indication of previous intake of vitamins than was the vitamin load test However, the question can be raised as to whether these conclusions would be valid for subjects on varied diets

The load test method has been based on the belief that subjects whose tissues are depleted of a certain vitamin will tend to retain a higher percentage of a test dose than will subjects whose tissues are saturated with the vitamin Johnson and co-workers[98] have reported that oral load tests are preferable to intravenous ones largely because absorption defects may be detected by the former method Lossy *et al*[99] examined the test dose excretion of 5 B complex vitamins in 39 essentially normal persons and 76 subjects of varying nutritional states They found significant correlations between inadequate intake and low excretion levels for thiamine riboflavin and N-methylnicotinamide while neither thiamine nor riboflavin excretion was significantly diminished in patients with clinical evidence of vitamin B complex deficiency

Urinary excretion results are of little value in grading the severity of a deficiency There has been considerable variation reported in the urinary excretion results from individuals supposedly under similar conditions

These divergencies may be explained in part by (1) individual variations due to differences in absorption from gastro-intestinal tract, (2) various renal threshold levels, (3) different levels of excretion due to differences in the rate and volume of urine excreted, (4) inadequate emptying of the bladder, (5) varying amounts of the test dose administered, and (6) different degrees of tissue breakdown as the result of the deficiency state. All of these factors must be considered when urinary excretion studies are used to evaluate the nutrient state. Sinclair[100] believes that since we know so little about the renal threshold and metabolism of these nutrients, estimations upon urine, with or without test doses, are not valuable for assessing nutriture. Johnson is more optimistic concerning urinary excretion methods, he feels that both a low excretion during fasting and a poor return after a test dose should be required for the chemical diagnosis of a deficiency state. The present consensus seems to be that excretion of water soluble vitamins does reflect body stores, and that excretion tests are of value in studying the nutritional state of the individual.

In addition to the use of urinary excretion tests for measuring the state of nutrition of the individual, Melnick, Hochberg, and Oser[101] have proposed a urinary excretion test to determine the physiological availability of the vitamins. The test is based upon the finding that in normal subjects, who are subsisting on adequate diets, the urinary excretion of the water soluble vitamins or their derivatives, parallels the quantity consumed. The linear-dose relationship found by feeding the vitamins in their most available form constitutes the basis of the assay for ascorbic acid, thiamine, riboflavin, and nicotinamide.

THIAMINE DEFICIENCY

Methods.—Thiamine excretion tests have been carried out either in the fasting state or for varying periods of time following oral or parenteral administration of this vitamin. Several methods have been developed for the determination of thiamine in urine. The chemical methods are based on two general reactions: (1) the oxidation of thiamine to thiochrome and measuring its fluorescence, and (2) the coupling of thiamine with a diazotized amine and the measuring of the intensity of the resulting color. Perhaps the most widely used procedure is to oxidize the thiamine to thiochrome which is then extracted into butyl alcohol and measured fluorometrically.[102] Najjar and Wood[103] have reported that there is present in urine an interfering fluorescent substance which they called F_2. This material has been identified as N-methylnicotinamide. There is now reason to believe that there are other extraneous substances in urine that also contribute to this fluorescence.[104] One of the most troublesome problems in the determination of urinary thiamine has been how to obtain a satisfactory blank. Bessey and co-workers[105] have designed a method which obviates butyl alcohol extraction and provides valid blanks obtained by treatment with benzene-sulfonyl chloride.

A colorimetric method by Alexander and Levi[106] uses p-aminoacetophenone which couples with thiamine to produce an insoluble purple-red compound. Such substances as uric acid and ascorbic acid interfere with

the development of the color The removal of these interfering substances is difficult The method also is not sensitive for material with a low content of thiamine While the azocoloric method is less sensitive and less specific than the thiochrome method it is simpler and quicker and hence may be useful for clinical determinations in urine[107]

Microbiologic methods have been developed for the determination of thiamine in urine using Lactobacillus fermentum 36[108] This procedure measures the stimulating effect of thiamine on the rate of alcoholic fermentation It has the advantage over the chemical methods in that it is unnecessary to digest the urine prior to determining the thiamine content The authors however recommend digestion for complete extraction and the conversion of cocarboxylase to thiamine The pyrimidine and thiazole moieties of thiamine show no growth-promoting activity up to eighteen hours of incubation but with longer incubation periods some activity is apparent This method lacks specificity and therefore tends to give somewhat higher values than do the chemical methods Burch *et al*[109] have designed a micro method for the measurement of total thiamine, free thiamine and thiamine phosphate in whole blood red blood cells, white blood cells, and serum This procedure is based on the conversion of thiamine to thiochrome and the measurement of the latter with a sensitive micro-fluorometer

Applications —Although the urinary excretion of thiamine is related to thiamine intake it is highly characteristic of the individual and high degrees of variability occur when the thiamine intake increases[93] The excretion of thiamine falls quickly when the intake is reduced However low excretion levels may exist for months before there is clinical evidence of a deficiency Stearns *et al*[111] studied the technique of using twenty-four-hour urinary excretion of thiamine as an assessment of thiamine nutriture in children and found it a reliable method for the detection of adequate thiamine intake From their data it would appear that the excretion of less than 10 per cent of the intake in the age group studied (4¾ to 13 years) indicates inadequate thiamine intake

The quantity excreted in a one-hour fasting sample gives some correlation with previous intake[112] There is considerable disagreement among various investigators however, as to what minimal excretion levels are indicative of a deficiency state Recommended levels range from zero excretion[113] to 4 micrograms in a one-hour period[112] Adamson *et al*[114] have found the excretion of thiamine to be related to the excretion of creatinine and that this ratio is fairly constant from voiding to voiding in any given individual Toulu and associates[110] studied daily thiamine excretion by subjects on controlled intakes of this vitamin and concluded that the determination of thiamine in micrograms per gram of creatinine in individual voidings as well as twenty four-hour samples could be used for a rough estimate of the status of thiamine nutrition

The load test method has also been used but there is considerable disagreement as to what level of excretion may be considered as indicating a deficiency state Holt[115] has reported that the thiamine excretion following the intravenous administration of 1 mg of the vitamin decreases to less than 50 micrograms in a four-hour period when associated with a

deficiency state Lossy *et al* [99] also found that thiamine excretion after the test dose was lower in those patients with signs of thiamine deficiency and low thiamine intakes than in the control group

The average total thiamine content of normal human whole blood is reported to be 4 7 ± 0 19 μg per cent Normally, red blood cells, white blood cells, and plasma contribute approximately 75, 15, and 10 per cent respectively of the total thiamine content of whole blood

Burch [109] noted that a dose of thiamine made little change in the amount of thiamine in blood, whereas there was the expected increase in urinary excretion Dube *et al* [116] used the Burch method to measure the blood thiamine content of subjects kept on controlled levels of intake, at 500 to 300 μg of thiamine per 1,000 Cal for a period of at least two weeks No subject had been in a state of inadequate thiamine nutrition according to urinary data [110] The subjects on the 300 μg of thiamine per 1,000 Cal had only slightly lower blood levels than those on the higher intake The administration of a 5 mg oral test dose of thiamine hydrochloride gave inconclusive evidence of a significant elevation of the blood level of this vitamin

Subsequently, Burch, in making biochemical measurements of the effect of the enriched rice program in Bataan, reported a significant increase in blood thiamine following the enrichment program That this increase in thiamine blood level could not be accounted for on the basis of an increased number of red blood cells was shown by the fact that there was also an increase in the thiamine concentration of the red blood cells

It would appear that useful data could be obtained from further study of the relation between the amount of thiamine found in different fractions of human blood and dietary intake It would also be interesting to study the influence of factors other than dietary intake on the level of thiamine in blood and its various cells

Goodhart and Sinclair[117] studied the amount of cocarboxylase in whole blood and found that it varied directly with the amount of total thiamine, as determined by biological methods, and also with the degree of tissue saturation The decarboxylation of pyruvic acid requires the coenzyme cocarboxylase (thiamine pyrophosphate), and a deficiency of thiamine has been found to result in an elevation of blood pyruvic acid The elevation of blood pyruvic levels, however, is not a specific indicator of thiamine lack since other pathological conditions are also associated with an increase in the amount of this substance in blood Except in severe thiamine deficiencies, the determination of fasting pyruvic levels in blood is not a reliable indicator of thiamine deficiency

Since both lactic and pyruvic acid are normally formed during carbohydrate metabolism, it was thought that the determination of the level and ratio of pyruvic and lactic acid in blood might be a reliable aid in evaluating thiamine nutrition [118] Horwitt and Kreisler[119] carried this reasoning a step further and proposed a test based on the fact that the rate of breakdown of pyruvic acid is directly related to the metabolic load of glucose and lactic acid Accordingly, the simultaneous determination of these three constituents under proper conditions seems to provide useful information regarding thiamine nutrition The technique is as

follows The subject is given orally 9 ml of 20 per cent glucose per kg of body weight after a fasting basal blood sample has been withdrawn After waiting sixty minutes, the subject walks up and down a flight of 21 steps each 19 cm high, in a period of one minute After five minutes blood is again drawn These values are then substituted into the following formula

$$\text{CMI (Carbohydrate Metabolic Index)} = \frac{L - \frac{G}{10} + 15P - \frac{G}{10}}{2}$$

where G, L, and P represent levels of glucose, lactic acid and pyruvic acid in milligrams per 100 ml of blood respectively The authors claim the upper limits of a normal CMI to be about 15

RIBOFLAVIN DEFICIENCY

Methods —Different methods have been developed for the determination of riboflavin in urine, based either on the use of microbiological or fluorometric procedures The latter methods involve measuring the fluorescence produced by the flavin in urine when subjected to light of prescribed wave lengths The fluorescence is measured either directly or after flavin has been concentrated by adsorption techniques (indirect) Najjar[120] has proposed a method that uses both the direct and indirect procedures Slater and Morell[121] have modified the latter method by (1) the introduction of an internal standard, (2) the use of larger amounts of oxidizing agent and (3) a controlled incomplete destruction of the riboflavin in solution The quantity of riboflavin in urine can also be assayed by measuring the rate of acid produced by Lactobacillus casei in a media in which riboflavin is the limiting factor for the organism With this method the urine is added directly to the culture tubes and the response determined by either acidimetric or turbidimetric means The biological method of Snell and Strong has been adapted by Strong *et al*[122] for determining riboflavin in blood and urine According to this method the riboflavin is first adsorbed on Lloyd s reagent and the adsorbate added to the culture tubes

A careful critique by DeRitter and associates[123] of methods used for the determination of riboflavin in urine revealed that there is good agreement between the Slater and Morell fluorometric method and the microbiological method of Snell and Strong even for urines with low riboflavin concentrations The high levels of urea which cause slight lowering of the titrimetric microbiological results can be avoided if the response is measured by the turbidimetric technique Najjar's fluorometric method and the microbiological method of Strong *et al* have both been adapted for the determination of riboflavin in blood A modification of the latter procedure has been made by Lowry and Bessey[124] which will detect concentrations as low as 0 5 to 2 0 millimicrograms of riboflavin They have reported using as little as 15 cmm of red blood cells for this determination

In general, the microbiological methods have not been very satisfactory for determining riboflavin in blood This has been due largely to the diffi-

culty in measuring the low concentrations of this vitamin associated with inseparable substances in blood extracts which either increase or decrease bacterial growth The microbiological procedures also do not differentiate between riboflavin and its derivatives

Because of the above difficulties, Burch and associates[125] developed a *micro-fluorometric* method for the determination of riboflavin in serum The method determines the three forms found in serum, namely free riboflavin, flavin-mononucleotide, and flavin-adenine-dinucleotide The determination of these flavin compounds depends on the following characteristics in a neutral solution, on a molar basis, riboflavin and flavin mononucleotide (FMN) exhibit the same fluorescence while flavin-adenine dinucleotide (FAD) is only about 14 per cent as fluorescent, and FAD and FMN are completely hydrolyzed by 5 per cent trichloroacetic acid This method requires the use of a very sensitive fluorometer Bessey *et al*[126] have developed a method for the determination of total riboflavin content of red blood cells Suvarnakich *et al*[127] have successfully employed the Farrand photoelectric fluorometer for the measurement of riboflavin and its *derivatives in blood*

Applications —Extensive and varied investigations have been carried out in the hopes of correlating urinary riboflavin excretion with nutritional status Some of the various methods employed have determined the amount of urinary riboflavin excreted in, for example, one hour while fasting,[97,113,128] during twenty-four hours[128,129] and after the administration of load tests[97,99,130] In reviewing the findings, one is impressed with the *variations in urinary riboflavin excretion in supposedly deficiency states* Likewise, there is no consistent agreement between workers in the interpretation of their results[98,99,130,131] It has been demonstrated that not only is the excretion of riboflavin affected by the dietary intake of this vitamin, but that such excretion is also proportional to the volume of urine excreted and inversely related to the level of protein intake[13]

The value of load tests in appraising riboflavin nutrition has not been settled,[98,128,133] although Hagedorn and co-workers[133] have *demonstrated* sufficient correlation between the amount of the supplement administered and the quantity excreted to justify the use of load tests

Using the microbiological procedure, Axelrod *et al*[134] detected no significant difference between the blood level of riboflavin in well nourished people and in those showing signs of riboflavin deficiency The significance of these results may be questioned on two premises First, it is known that there are substances *in blood that may enhance or inhibit bacterial growth*[135] and hence may have interfered with the accuracy of the results Second, since the formed elements contain on an average 274 *μg per cent of total* riboflavin,[125] any change in the number of blood cells may have masked alterations of the total serum riboflavin Burch and associates[125] and Suvarnakich *et al*[127] used the microfluorometric technique and reported serum riboflabin values for normal subjects as 0 84, 2 32 and 3 16 *μg* per *cent for free riboflavin*, flavin adenine-dinucleotide (FAD), and total riboflavin respectively Age and sex were not factors causing serum level variations There *was a wide variation for* serum riboflavin values, standard deviations of 0 71 *μg* per cent, while this deviation was only 0 42 *μg*

per cent for FAD The greater stability of serum FAD suggests that it might be a diagnostic aid if it can be correlated with nutritional status Mann and fellow-workers[136] and Burch *et al*[15] reported correlations between riboflavin intake and serum levels of FAD in animals Similar results have been published by Suvarnakich and associates who assumed that human serum FAD indicates riboflavin nutriture and is a diagnostic aid in determining a state of riboflavin deficiency However, their study of daily riboflavin supplementation gave no conclusive results They reported that nitrogen balance and riboflavin intake had no significant effect on serum riboflavin levels providing sampling was done several hours after the vitamin was ingested The significance of finding the serum FAD levels higher than normal in cases of cardiac disease and hypertension remains an enigma Bessey *et al*[16] have found that total riboflavin content of the red blood cells serves as the most practical and reliable means of evaluating riboflavin nutritive status They conclude that a red blood cell riboflavin content of 20 μg/100 ml indicates an adequate intake Plasma free riboflavin plus FMN does reflect dietary intake but the above investigators consider it a less reliable index of dietary intake

NIACIN DEFICIENCY

Methods —The fact that nicotinic acid (Niacin) is one of the most stable of the known vitamins makes possible the use of strong acids and alkali in extracting and hydrolyzing various niacin derivatives A popular method for the determination of nicotinic acid is based on the color produced when a pyridone derivative reacts with cyanogen bromide and an aromatic amine (König reaction) Since the intensity of the color produced by equivalent amounts of nicotinic acid and the amide is not equal the amide is usually hydrolyzed to the acid and measured as nicotinic acid N methylnicotinamide is stable to this hydrolysis and does not give the color reaction Rosenblum and Jolliffe[137] following the Bandier and Hald method developed a simple and specific procedure for the determination of nicotinic acid and its amide in urine by using p-methylaminophenol sulfate as the aromatic amine The color produced by this amine is more stable than that produced by the aniline used in the Bandier and Hald procedure

The determination of nicotinic acid and the methyl derivatives (N^1-methylnicotinamide and trigonelline) is carried out in several ways According to one method the N^1 methylnicotinamide is extracted adsorbed eluted and its fluorescence determined in alkaline solution This determines only N^1-methylnicotinamide and perhaps some closely related substances exhibiting fluorescence Another method consists in changing the N^1-methylnicotinamide in dilute alkali to trigonelline degrading the latter to an open ring structure and adding an aromatic amine to produce a color This procedure determines both N^1-methylnicotinamide and trigonelline A third general procedure is to convert trigonelline to nicotinic acid by hydrolyzing with strong alkali in a solution of urea and determine it colorimetrically With this procedure nicotinic acid N^1 methylnicotinamide and trigonelline are determined The fluorometric methods used

to determine the amount of N^1-methylnicotinamide in urine are those proposed by Najjar,[138] Huff, and Perlzweig,[139] and Hochberg, Melnick, and Oser [140]

Sarretts' modification[141] of the Kodicek and Wang procedure is commonly used for the determination of urinary N^1-methylnicotinamide and trigonelline Benzidine is the aromatic amine used to develop the color Trigonelline is a non-vitamin compound found in considerable amounts in certain foods and excreted unaltered in the urine, therefore, a method that determines trigonelline along with nicotinamide cannot be used to estimate vitamin intake

Knox and Grossman[142] demonstrated that N^1-methylnicotinamide is metabolized to N^1-methyl-6 pyridone-3 carboxylamide (commonly referred to as pyridone) and excreted in urine in appreciable amounts after the ingestion of nicotinamide Rosen, Perlzweig, and Handler[143] considered this compound to be the end product of nicotinamide metabolism, the amount excreted in the urine being proportional to the vitamin intake

Rosen and associates[144] have developed a fluorometric method for determining pyridone in urine This method consists of clearing the urine with basic lead subacetate, extracting the pyridone with ether from the lead filtrate saturated with K_2CO_3, evaporating off the ether and taking up the residue in acetone, agitating the acetone with small amounts of KOH and fluorometric estimation of the pyridone The pyridone can also be determined spectrophotometrically, if the residue remaining after evaporation is taken up in water rather than acetone With this procedure, N^1-methylnicotinamide does not interfere with the determination of pyridone

Stotz[145] developed a clinical method for the determination of total nicotinic acid (free and bound) in blood and urine which depends upon the reaction between nicotinic acid, cyanogen bromide, and p-aminophenol Five ml of oxalated blood or 15 ml of urine are required Melnick and Field[146] described a method for blood based upon charcoal adsorption and coupling with aniline as the amine This method is not well adapted for clinical use

Microbiological methods have been applied to the determination of nicotinic acid and nicotinamide in whole blood, serum, spinal fluid, and urine Various kinds of test organisms have been used, such as L arabinosus[147] and Shigella paradysenteriæ [148] Isbell and associates used the latter organism They recorded growth response in terms of so many "equivalents to nicotinamide" This term is used because the organism responds not only to nicotinamide but also to nicotinic acid and a number of other related compounds, so that the value obtained can be taken only as a relative and not an absolute measure of nicotinamide This fact of course, makes quantitative comparison with results obtained by chemical tests impossible

Applications —The average concentration of nicotinic acid in red blood cells of man has been reported to be 13 μg per ml ,[149] mostly accounted for by pyridone nucleotides The nicotinic acid content of plasma averages 0 3 μg per ml It is necessary that values for whole blood be recorded in terms of red cell concentration

Unfortunately, the concentration of nicotinic acid in the blood, determined biologically or chemically, fails to show reasonably close correlation with the intake of nicotinic acid or with the signs and symptoms of deficiency[150] Patients with pellagra have been shown to have levels little if any lower than those reported for normal subjects Likewise, there appears to be no significant relationship between co-enzyme concentration in the blood and signs of niacin deficiency[151 152]

At the present time more information is needed on blood levels, both on cellular elements and whole blood Until such information is available, blood levels cannot be of much assistance in evaluating niacin nutrition

It appears that the determination of N methylnicotinamide in urine is the most practical laboratory procedure for determining niacin nutrition, however, workers disagree on what per cent of the niacin intake is excreted as N¹ methylnicotinamide[153] They also have diverging views regarding the significance of twenty-four-hour urinary excretion studies One group contends that the determination of N¹-methylnicotinamide for a twenty-four-hour period is of little help in evaluating niacin nutrition[154] Another group feels that there is reasonably good correlation between the excretion of this compound and dietary and clinical findings[155]

In normal subjects there is a maximum increase in the excretion of N¹ methylnicotinamide two to four hours after the administration of the test dose Johnson[98] has stated that if four hours following the administration of a 50 mg test dose of niacinamide the excretion is 0 5 mg or less, then there is evidence of chemical inadequacy The test dose excretion of N¹-methylnicotinamide has been studied by Lossy, Goldsmith, and Sarett,[99] who report less excretion of this substance in normal control groups than in those with signs of thiamine or vitamin B complex deficiencies

The different findings in different studies undoubtedly are due in part to the variety of methods used, as well as to inter- and intra individual variations The differences in the bodies' methylating ability may also partly account for variance Since it is now established that tryptophan is a precursor of niacin it is possible that this conversion process may be another cause for variations noted in excretion studies

Holman and DeLange[156] determined the amount of N methylnicotinamide and pyridone excreted in the urine of a normal adult male during three-hour intervals over a twenty four-hour period Throughout the day 6 3 mg of N¹ methylnicotinamide and 14 2 mg of pyridone were excreted Following load test doses of niacin and niacinamide there were much larger amounts of end products recovered from the urine after the administration of niacinamide than after niacin The authors expressed the opinion that amidation is an important factor regulating the production of metabolites excreted in the urine They also presented additional evidence that tryptophan is a precursor of niacin, and that its administration results in an increased excretion of N¹ methylnicotinamide and pyridone The administration of amino-acid mixtures containing only traces of niacin and tryptophan did not result in an increased excretion of the above metabolites Frazier *et al*[157] studied the levels of excretion of nicotinic acid metabolites in relation to intakes of the vitamin and tryptophan by human subjects On a control diet of 11 3 mg of the vitamin and

885 mg of tryptophan, the average amount excreted as the vitamin, N-methylnicotinamide and pyridone, balanced the intake Basal diets containing less nicotinic acid or tryptophan resulted in a decrease in the total excretion of the vitamin and its metabolites

There is an acute need for more accurate methods for estimating body stores of niacin and for evaluating the recent intake of this vitamin Perhaps studies of the combined excretion of N^1 methylnicotinamide and pyridone may give new light on this problem At present, the excretion levels of N^1-methylnicotinamide in the urine during fasting and after administration of load test doses of niacin are perhaps the best chemical procedures available for appraising niacin nutrition

TEST FOR OTHER B VITAMIN DEFICIENCIES

Vitamin B_6 —Scudi, Koones, and Keresztesy[158] developed a colorimetric method for determining pyridoxine in urine based upon the reaction between pyridoxine and 2,6 dichloroquinone chlorimide This method is not satisfactory for urine with low concentration of pyridoxine since various urinary substances interfere Pyridoxic acid can be determined by the method of Huff and Perlzweig[159] At the present time there is some *question as to whether this fluorometric method measures only 4-pyridoxic* acid Fujita and co workers[160] have recently developed a more specific and exact fluorometric method for the analysis of pyridoxic acid in urine In addition, they have designed certain adsorption techniques which make possible the determination of other pyridoxine metabolic products in urine These methods should greatly improve our armamentarium for the study of the metabolism of this vitamin Microbiological methods such as described by Atkin *et al*,[161] also have been used to measure vitamin B_6 in urine

Spies *et al*[16] *reported that, following the intravenous administration of* 50 mg of pyridoxine normal persons excreted approximately 8 per cent of the total dose in twenty-four hours, while patients with clinical signs of pellagra, beriberi or riboflavin deficiency excreted on the average 0 5 to 1 5 per cent of the total dose in twenty-four hours Studies by Linkswiler and Reynolds,[163] on urinary and fecal elimination of vitamin B_6 and pyridoxic acid, indicated that the latter accounted for 77 per cent of the total elimination and 95 per cent of the urinary excretion *Holt and co-*workers[165] placed infants on pyridoxine-free diets and noted a failure of pyridoxine *products to appear in the urine* associated with anemia and retardation of growth

One function of this vitamin is to form pyridoxal 5 phosphate (B_6-PO_4) which serves as a coenzyme for a wide variety of biochemical reactions involving amino acids Boxer and associates[164] have compiled data on the content of B_6-PO_4 in human whole blood and isolated white blood *cells* The method used is one based on the activation of tyrosine decarboxylase by B_6-PO_4 The *clinical significance* of such measurements remains to be demonstrated

Xanthurenic acid is excreted in human beings who are deficient in pyridoxine, especially if the diet is high in tryptophan Therefore, a

tryptophan load test has been designed to detect a deficiency of pyridoxine.[166] Such a test involves collecting a 24 hour urine specimen for control levels of xanthurenic acid excretion, then administering orally 10 grams of racemic tryptophan and collecting another 24-hour specimen. An increase in xanthurenic acid excretion indicates a pyridoxine deficiency.

Pyridoxine or its metabolites is believed to serve as a prosthetic group for transaminase enzymes in man. Isonicotinic acid hydrazide (INH) has been shown to produce a pyridoxine deficiency in man by probably forming an INH-pyridoxine complex. Sass and Murphy[167] have demonstrated a significant decrease in the whole blood glutamic-oxalacetic transaminase (G.O.T.) after the daily ingestion of 500 mg. of INH for 6 to 11 weeks of therapy. Transaminase levels returned to normal after the administration of 25 mg. of pyridoxine per day. These workers feel that blood G.O.T. activity may reflect pyridoxine deficiency before detection by the tryptophan load test.

Pantothenic Acid.—Various microbiological methods have been applied to the measurement of this vitamin in urine and blood.[168–170] It may be determined by using any one of a group of lactobacilli. Usually L. casei is selected for this measurement.[171] Since pantothenic acid occurs in blood and urine in a bound form unavailable for growth of yeast, it is necessary to free it from its conjugates (co-enzyme A) by either autolysis or a mixture of alkaline phosphatase and liver enzyme action before a determination is made.

Studies by Spies and associates on patients with multiple B complex deficiencies revealed that there was a 25 to 50 per cent reduction in the blood levels of this vitamin in these patients as compared with normal subjects. They also exhibited a lowered urinary excretion. Stanberry and Spies[88] noted that following intravenous injection of 50 mg. of dextrorotary calcium pantothenate the average excretion of persons with vitamin deficiencies was 19 per cent, whereas the average excretion of controls was 102 per cent of the dose administered. Urinary excretion of pantothenic acid has been reported to be reduced in patients with liver disease.[172]

Biotin.—Microbiological methods have been applied to the determination of biotin in blood and urine.[173,174] Such organisms as Saccharomyces cerevisiæ and Lactobacillus casei have been used for these measurements. The amount of growth is determined by titration of the acid produced.

Oppel[174] noted that normal subjects excreted from 14 to 100 micrograms of biotin per day. The total biotin output in urine and feces was 3 to 6 times greater than the intake. In addition to the rather large amounts of free biotin in human urine, Wright *et al.*[175] have reported small quantities of a hydrophilic biotin derivative which may be biocytin sulfoxide. During starvation the excretion levels of biotin are not abnormally low.

Folic Acid and Citrovorum Factor.—Biological methods have been designed for determining folic acid in the urine.[176,177] Either L. casei or Streptococcus fecalis R is used for this purpose. Digestion of the urine sample with an enzyme is not necessary since this vitamin is excreted in the urine in the free form.

The citrovorum factor has likewise been assayed by biological methods[177] using the Leuconostoc citrovorum organism. The extent of growth is measured by the amount of acid produced.

Register and Sarett[179] reported an average urinary excretion of folic acid by human subjects on various diets of approximately 4 μg per day with a range of 2 to 7 μg. Those individuals on a high purine diet exhibited a higher excretion.

Broquist and co-workers[180] have stated that the average amount of citrovorum factor excreted in normal urine is somewhat less than 0.001 μg per ml. Six hours after the oral administration of 50 mg. of folic acid to normal subjects, 0.1 per cent of this substance was converted to citrovorum factor. Ascorbic acid appears to increase the excretion of this factor following the administration of folic acid.[181, 182]

Formiminoglutamic acid, an intermediate in the metabolism of histidine, has been shown to accumulate in the urine in folic acid deficiency in man.[183] Urinary formiminoglutamic acid has also been noted to be increased in patients treated with folic acid antagonists[184] and in macrocytic anemia of pregnancy. The increased excretion of this compound is attributed to a deficiency of tetrahydrofolic acid which is required for the metabolism of formiminoglutamic acid. Tabor and Wyngarden have designed a sensitive spectrophotometric method for the assay of formiminoglutamic acid in urine.[185]

Vitamin B_{12}.—Many of the procedures used in the assay of B_{12} in animal material have been biological ones.[186–188] The Lactobacillus leishmanii organism is usually used for this determination. The rate of growth is measured either turbidimetrically or by the amount of acid produced. Boyer and Richards[189] have designed a chemical method based on the determination of 5,6 dimethylbenzimidazole (a product resulting from the acid hydrolysis of vitamin B_{12}) by colorimetric and fluorometric methods.

Register and Sarett[179] reported an average daily excretion of 31 millimicrograms in subjects on a normal diet. Chestermann *et al.*[190] noted that in normal males with intramuscular injections ranging from 5 to 1000 μg of vitamin B_{12}, the relationship between dose given and amount excreted could be expressed by the following equation: E (amount excreted in eight hours) = D (dose injected) − $1.2D^{0.89}$. Sokoloff[191] and associates reported an increase in the percentage elimination of 30 to 45 μg doses of vitamin B_{12}, if previously larger amounts of the vitamin had been given, *i.e.*, there was evidence of saturation. Chow *et al.*[192] observed that, after intramuscular injection of this vitamin, the largest amount was excreted within eight hours. Chestermann and collaborators[190] found that pernicious anemia patients excreted a lower percentage of the test dose than did normal subjects and that continued daily injection did not increase the urinary output of B_{12} to the extent noted in normal persons. Following the oral administration of 500 μg of vitamin B_{12}, Chow *et al.*[192] detected no vitamin B_{12} in the urine of either normal controls or pernicious anemia patients. Chestermann *et al.*[190] have likewise found that, following oral doses, insignificant amounts were excreted in the urine during a twenty-four-hour period. No significant increase was noted in the urinary excretion of this vitamin in normal subjects or pernicious anemia patients after the oral administration of as much as 10,000 μg. Little is known concerning the fate of ingested vitamin B_{12}. Ungley[193] has postulated that perhaps one reason for the low urinary excretion following oral ingestion is that a

large per cent of the vitamin is converted to a bound form after absorption from the intestine, and that this bound form is not readily excreted by the kidneys.

Ross,[194] using the Euglena gracilis method of assay, reported the vitamin B_{12} concentration of the blood to be between 350 to 750 μμ gm. per ml. Boger *et al.*[195] examined 528 normal persons and found serum levels varying from 70 to 1,060 μμg./ml. The serum level is reported to increase following injection of the vitamin.[194,196]

Tissues from patients with pernicious anemia exhibited vitamin B_{12} activity. No such activity, however, could be demonstrated in those tissues taken from patients who died of the disease.[197]

Today clinically little use is made of the serum concentration of this vitamin. This is because rather delicate microbiological techniques are required and because there is wide variability in normal serum levels. At present, radioactive tracer studies are preferred. Since vitamin B_{12} contains cobalt, it can be made radioactive. When labelled vitamin B_{12} is orally administered to normal persons, radioactivity found in feces indicates the amount not absorbed. Another procedure involves administering an oral dose of radioactive vitamin B_{12} and then measuring the amount of radioactivity stored in the liver by placing a scintillation detector over this organ.[198] Most commonly used clinical methods involve urinary excretion studies. One of the popular procedures is that devised by Schilling.[199] This test is based upon the principle that if a large amount of vitamin B_{12} is introduced into the blood at one time, then the blood level will exceed the renal threshold and the excess will appear in the urine. Since there is no selective excretion of labelled and non-labelled material, the vitamin B_{12} originally present in the blood will be proportionately excreted along with the added excess.

There are different modifications of this test. A common procedure is to administer orally 1–2 μg of radioactive vitamin B_{12} and approximately one hour later give about 1 mg. of unlabelled vitamin B_{12} by injection. This injected vitamin B_{12} raises the serum level to exceed the renal threshold and thereby "washes out" the vitamin B_{12} in the blood. If there has been absorption of the orally administered labelled vitamin B_{12}, then radioactivity will appear in the urine when the washing out dose is given and may be detected by radioactivity measurements.

Patients with pernicious anemia excrete very small amounts of labelled vitamin because of impaired absorption due to a lack of the intrinsic factor. If these patients are given an intrinsic factor preparation along with labelled vitamin B_{12}, then the excretion of radioactive B_{12} increases, indicating improved absorption. It is interesting to note that patients with achlorhydria *per se* do not have impaired absorption of vitamin B_{12}.[200] The hematological response to a test dose of vitamin B_{12} is also a good indication of the body's need for the vitamin.

ASCORBIC ACID DEFICIENCY

Methods.—Numerous methods exist in the literature for determining ascorbic acid. The most widely used ones are based upon the oxidation-

reduction properties of ascorbic acid. The reduction of a dye, most commonly 2,6-dichlorophenolindophenol, by the reduced form of ascorbic acid is the basis for many satisfactory methods. Titration[201,202] and colorimetric[203–205] techniques using this dye have been used in analyzing blood and urine; however, pigments and extraneous reducing substances in urine and blood interfere with the determination.

The dye reduction method measures only the reduced form of the vitamin. Since ascorbic acid is known to exist in the body both as the oxidized and reduced form, they do not determine total ascorbic acid. Roe and Kuether[205] have developed a method for determining total ascorbic acid in blood and urine based on the oxidation of ascorbic acid to dehydroascorbic acid and then reacting it with 2,4-dinitrophenylhydrazine to form a hydrazone which develops a red color when treated with concentrated sulfuric acid. Bessey, Lowry, and Brock[206] used the hydrazone technique to develop a micro-method for measuring ascorbic acid in blood and its various formed elements. This method recently has been modified, eliminating the need for specifically prepared carbon black.[207] Butler, Cushman and MacLachlan[208] designed both a macro- and micro-method for the determination of ascorbic acid in whole blood and its elements, using methylene blue. Numerous modifications of existing methods have appeared in the literature within the past few years, but few of them seem to possess any real advantages over established procedures.

Applications.—Johnson *et al.*[97] reported good correlation between the fasting excretion of ascorbic acid in the morning and the previous dietary intake. Increased amounts of ascorbic acid are excreted in the urine with increasing intake. A sudden increase in the per cent excreted has been reported to occur at serum levels of 1.0 to 1.2 mg. per 100 ml. (so-called "renal threshold"). King[209] has summarized controlled depletion experiments by stating that a decline in urinary excretion occurs within a few days on a diet depleted of ascorbic acid and that it continues throughout weeks and months, approaching "zero" excretion. Goldsmith has averred that the ascorbic acid excretion results in fasting urine should be conservatively interpreted.

A wide variety of load test methods for the analysis of ascorbic acid nutrition have been proposed.[150] In general, individuals with low intakes of ascorbic acid excrete less of a given dose than do those on an adequate or saturating intake.[210] The load test provides a fairly good index of tissue depletion and parallels moderately well the fasting plasma levels.[150] However, the load test does not distinguish between varying degrees of deficiency states. Lowry and colleagues[211] have proposed that the sensitivity of load tests may be increased if larger doses are administered. Sinclair has suggested that until we know more about the metabolism of ascorbic acid and its renal threshold, we should view with caution the results of load tests.

Estimation of ascorbic acid in serum reflects in general the immediate past intake of this vitamin.[74,1] If there have been liberal intakes, 75 to 100 mg. daily, the levels of ascorbic acid in the sera from fasting individuals generally will fall in the range of 1.0 to 1.4 mg. per cent, while individuals receiving 15 to 25 mg. will have levels ranging between 0.1

to 0.3 mg per 100 ml[213] However, the serum level response to a given intake will vary considerably from one individual to another. It is also well known that infection and other pathological conditions will influence the level of serum ascorbic acid. Athletes following intense and moderate exercise, are also reported to have significant reductions in their plasma ascorbic acid levels[14] Low blood ascorbic acid levels have been reported for aged healthy men and women on daily intakes of 30–35 mg[15] Ramsay and associates noted chronic mental patients of all ages had low blood ascorbic acid content and tissue unsaturation when on adequate ascorbic acid intakes[16] How low the level of serum ascorbic acid can drop and still be compatible with adequate tissue content is debatable. Some investigators consider blood values between 0.3 and 0.7 mg per cent to be the lower limits of normal. If such is the case then a considerable section of this country is in a deficiency state[217] It is perhaps more accurate to consider plasma ascorbic acid levels to reflect recent dietary intake rather than tissue saturation. It is possible to have zero levels of plasma ascorbic acid and still not exhibit clinical signs of ascorbic acid deficiency[210]

Crandon *et al*[18] noted that when individuals were placed on a diet that produced scurvy the plasma ascorbic acid reached zero after forty-one days but about twice this length of time was required to reduce the leukocyte ascorbic acid content to zero. Soon thereafter clinical signs of scurvy appeared. Lowry and co-workers[11] studied the interrelationship of dietary serum white blood cell and total body ascorbic acid. Diets of 78 mg per day gave approximately 90 per cent tissue saturation while with intakes between 8 to 23 mg of ascorbic acid per day, the white cell concentration decreased to values half of normal and serum concentrations ranged between 0.1 to 0.4 mg per cent. Linghorne *et al*[19] carefully studied the gums of the subjects receiving 8 to 23 mg of ascorbic acid per day and concluded that their resistance to mechanical trauma and bacterial invasion was decreased. Lowry has reported that with somewhere between 60 and 90 per cent tissue saturation handicaps related to ascorbic acid deficiency become evident. In view of the above observations it would appear that plasma levels more correctly reflect the recent dietary intake while white blood cell levels reflect the tissue content.

At present considerable controversy exists concerning the value of results obtained by using the above methods in detecting early stages of a deficiency state. Low excretion and low tissue concentration precede chemical and physical signs of impaired function. There are abundant indications that the health of tissues is significantly handicapped when the concentration of ascorbic acid is low in the tissues even prior to onset of physical signs of scurvy. Additional information is needed in order to evaluate or detect the lesser degrees of tissue desaturation[10]

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Chapter 17—(*Continued*)

B Roentgen Signs of Nutritional Deficiencies

By BERNARD PIERRE WIDMANN

ROENTGENOLOGIC evidence of deficient calcification of osteoid tissue is readily demonstrable in rickets scurvy and osteomalacia, and, after diet regulation, the progress of repair may be recorded with considerable accuracy The character and the degree of bone alterations in nutritional disease are commensurate with the duration and the extent of the dietary deficiency Roentgenologic findings in the small intestine are definite and typical and have proved of diagnostic value in supplementing or confirming clinical and physical evidence of nutritional disease

An attempt will be made to summarize in detail some of the roentgenologic findings in nutritional diseases with respect to (1) changes involving the bone, *i e*, rickets scurvy and osteomalacia and (2) changes in the small intestine which constitute the so-called "deficiency pattern"

ROENTGEN SIGNS OF BONE CHANGES IN DEFICIENCY STATES

Rickets —Rickets may be demonstrated in roentgenograms from birth to puberty Maxwell[1] has demonstrated its presence at birth in the babies of osteomalacic women in China The roentgenologic findings are changes resulting from calcium deficiency and are commonly seen about the wrists the ankles the knees and the anterior ends of the ribs

The changes are manifested in the metaphyses The outline is blurred and indistinct as a result of the deficient calcium salts The joint is hazy and the epiphyseal line of growth becomes broadened In older children bone trabeculation may be accentuated Decalcification of the metaphysis results in a concave "saucer" deformity (Figs 29 and 30) accentuated by a widening and splaying of the cortical margins as a result of softening and the stress of movement The concave saucer like appearance of the epiphyseal end of the diaphysis becomes irregular roughened and somewhat spiculated[2] The anterior ends of the ribs may be club-shaped roughened and broadened The cranial bones may present a woolly or coarsened appearance and show delayed closure of the sutures and fontanels Kyphosis, scoliosis and rib deformities are frequent complications Fractures of long bones are commonly found and are usually greenstick in type Rickets and scurvy may occur concomitantly Adolescent or renal rickets cannot always be differentiated from rickets due to vitamin D deficiency

The results of treatment are beautifully portrayed in serial roentgenograms by calcium deposition near the epiphysis A thin line of bone appears

between the diaphysis and epiphysis Fine white lines of density across the shaft of a bone that has grown during the active stage of the disease may indicate the duration of the process Periostitis of the fibula may be seen in severe cases, but is often simulated by the increased density of recalcification of the cortical structure The zone of repair is of greater density and smoother than the shaft, but the trabeculations are less distinct

Idiopathic Steatorrhea —Idiopathic steatorrhea, or celiac rickets (Gee's disease), is a predominant cause of osteomalacia Roentgenologic studies show the characteristic decalcification and deformities of bone found in osteomalacia Opaque enema studies frequently reveal a dilated, elongated, atonic type of colon



Fig 29 Fig 30

Fig 29 —Rickets showing characteristic 'saucer' deformity zones of provisional calcification

Fig 30 —Rickets showing bowing of lower extremities

Renal Rickets —Renal rickets, a result of chronic renal disease in children and altered calcium metabolism, may show roentgenologic changes very similar to those in rickets resulting from a vitamin D deficiency Brailsford roentgenologically classifies celiac rickets and renal rickets as true rickets The roentgenologic findings are therefore considered according to the description of the bone changes seen in rickets

Scurvy —Scurvy is not difficult to recognize Bone atrophy, microscopic fractures, and subperiosteal hemorrhages which readily calcify are predominant roentgenologic features[3] Suspected clinical evidence of trauma about the elbow, wrist, and joint regions is frequently revealed to be an effect of scurvy

The roentgenogram shows varying degrees of transparency of the bone structure, with resulting indistinctness of the bone trabeculations, especially near the ends of the diaphyses The cortex is thin and pencil-lined, and the increased transparency of the bone has a 'ground glass' appearance A similar dense ring around the epiphyseal center results in the same ground glass appearance of the central nucleus as shown in the diaphysis (Fig 31)



Fig 31 —Scurvy Diminished density and loss of normal bone pattern crushing effect at ends of bones with spur formation and beginning evidence of subperiosteal hemorrhage

A very dense zone of temporary calcification, the 'Trummerfeldzone, develops in the metaphysis just at the epiphyseal line This results from multiple small fractures and from calcification of the cartilaginous matrix Decalcification and radiolucence behind this zone occur in varying degree according to the duration of the disease The appearance of impaction and crushing of bone is accentuated by the spurlike contour of the diaphyseal

extremity Lateral displacement of the epiphysis and the adjacent dense zone at the end of the shaft repairs with good alignment after dietary control

Subperiosteal hemorrhages in the lower third regions of the shafts of the bones may be detectable as fusiform soft tissue densities but generally appear as calcifications after treatment (Fig 32)

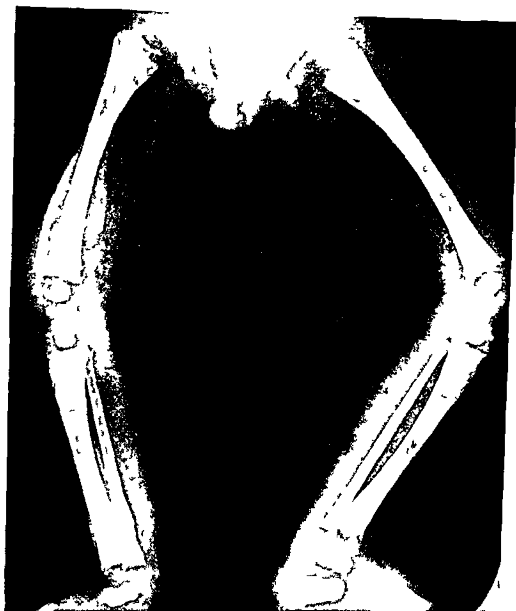


FIG 32 —Scurvy, with repair and calcification of subperiosteal hemorrhage

In the process of repair, new bone formation develops at the epiphyseal line The "Trummerfeldzone" diffuses into the shaft with resulting transverse lines of density The generalized effects of osteoporosis disappear Scurvy and rickets may occur in the same patient

Kato [6] published a lengthy analysis of these roentgen signs of infantile scurvy and concluded that none of them is pathognomonic except the sub-

periosteal hemorrhages The increased density of the zone of temporary calcification is found in congenital syphilis and in healed rickets, as well as in lead and other heavy metal poisoning Zones of lessened density behind the zones of temporary calcification are also found in congenital syphilis and leukemia *The roentgen appearance of bone atrophy in scurvy is a composite picture* and the diagnosis is based on concomitant changes

Park[27] and his associates described what is probably the earliest roentgenographic manifestation of scurvy a slight fuzziness of the cortex at the distal outer border of the diaphysis with rarefaction of the neighboring cancellous tissue *This defect enlarges as the disease progresses* Park called this sign 'fuzzing ' Others in referring to it have termed it the corner sign ' *This is probably one of the earliest, if not the earliest, sign of scurvy*

Osteomalacia —Osteomalacia may be related to a diet deficient in vitamin D and calcium salts or to faulty absorption with resulting idiopathic steatorrhea The roentgenologic changes are essentially an effect of a deficient calcification of the osteoid tissue and resemble those of rickets to a striking degree

The radiolucence of the bone structure varies according to the extent of the disease Advanced cases show a degree of decalcification that results in a bone density equal to that of the surrounding soft tissues *The bone outline is traceable by a thin pencilled margin* There is softening and bending as a result of muscle and weight strain and multiple fractures are common The pelvis, hip joints, and long bones, as well as the spine and ribs, are subject to marked deformities Cystic areas may replace absorption of cancellous tissue at fracture sites Multiple sharply defined skull rarefactions may resemble myeloma The normal base line of the skull may be altered *as a result of bone softening*

THE ROENTGENOLOGIC MANIFESTATIONS OF NUTRITIONAL DISEASE IN THE SMALL INTESTINE

Abnormality of the small bowel outline in a case of nontropical sprue was described by Mackie[4] Changes in the contour, motility and mucosal pattern were noted in a series of cases of chronic idiopathic steatorrhea by Snell and Camp[5] They observed 'alterations in the mucosal relief of the small intestine especially the jejunum consisting of smoothing of the contours of the lumen, obliteration of the usual markings of the valvulae conniventes and clumping of the barium in elongated masses occurring in all cases in which adequate roentgen observation was possible during the active stage of the disease '

This description of the small intestine has been corroborated by all subsequent observers of the roentgenologic changes in deficiency disease Snell and Camp did not believe these findings were pathognomonic roentgenologic evidence of a deficiency disease, as subsequent experience of others has shown Tropical sprue was found to cause marked abnormality of contour and motility in the small intestine (Mackie and Pound[6]) and in the same year (1935) these appearances were noted in ulcerative colitis by Mackie Miller and Rhoads[7]

During the past eight years, abundant roentgenologic evidence has accumulated to show that the small intestine pattern may be definitely altered in patients with nephrosis, diabetes insipidus, hypocalcemia, acholia, or infantile celiac syndrome, and in newborn infants

Similar changes may be detected in routine roentgen studies where definite, or possibly vague, atypical abdominal symptoms exist but without any definite clinical findings that may be related to nutritional disease It has now been demonstrated, and is generally recognized, that abnormal small-bowel contours may be found in a wide variety of pathologic entities, *i e*, peptic ulcer, malignant neoplasm, and many *other conditions* possibly related to reaction to inflammation of the gastro intestinal tract Pancreatic disease, biliary disease, regional ileitis, myxedema, protracted diarrhea, migraine, allergy, and tuberculosis of the small intestine have been noted to present so-called "deficiency patterns" of the small intestine in routine x-ray examinations

The only proof that the roentgenologic changes are an effect of deficiency disease is clinical evidence of improvement after specific therapy The clinical response to vitamin therapy may be very rapid and definite, but changes in the small-bowel contour may persist to a moderate degree Deficiency states may exist without any demonstrable roentgenologic evidence

The so-called "deficiency pattern" or abnormal distribution of barium in the small intestine in nutritional disorders may be considered evidence of either *primary* deficiency, as when the only evident factor is a possibly deficient diet, as in pellagra or sprue, or *secondary* deficiency, as when there is obvious organic disease of the gastrointestinal tract or some other region

The list of diseases or clinical entities known to cause the alterations in the appearance and function of the small intestine known as the "deficiency pattern" are classified by Krause and Crilly[8] as follows

I *Nutritional disturbances*
- A Primary (no obvious anatomic cause)
  1 Celiac disease
  2 Tropical sprue
  3 Nontropical sprue (idiopathic steatorrhea)
  4 Deficiency disease (as pellagra)
- B Secondary to disease of the gastrointestinal tract
  1 Peptic ulcer
  2 Cancer
  3 Tuberculosis of the small intestine
  4 Biliary or pancreatic disease
  5 Chronic ulcerative *colitis*
  6 Regional ileitis
  7 Sclerosing inflammation of the mesenteric lymphatics

II *Other causes*
  1 Hypoproteinemia (as nephrosis)
  2 Diabetes insipidus
  3 Parathyroid disease
  4 Allergic states
  5 Hookworm *infestation (Necator americanus)*
  6 Generalized amyloidosis

Normal Roentgenologic Appearance of the Small Intestine.—Studies of e roentgenologic alterations in the mucosal pattern have been of great portance. Notable contributions on the value of recognizing changes in e mucosal outline in disease have been made by Akerlund,[9] Berg,[10] aoul,[11] Forssell[1] and Cole.[13] Their experiences and observations have en monumental in laying the groundwork for the present special interest in the correlation of clinical and physical findings with roentgenologic gastroscopic pathologic and experimental data. Much additional experience will be necessary before agreement can be reached concerning the interpretation of phenomena now observed roentgenologically.

Excellent studies on the roentgenologic outline of the normal small intestine have been made by Pendergrass, Ravdin, Johnston and Hodes[14] and Pendergrass and Comroe.[15] These investigators have submitted very convincing evidence of the so-called "normal small bowel pattern" as related to the outline of the mucosal folds, contour and motility, as well as the effect of different suspension mediums for the barium sulfate, i.e., glucose, fat and various flavoring extracts. There is considerable variation in the normal outline; the distribution of the barium is regular and the caliber of the bowel is almost uniform in width except for intermittent fleeting contractures resulting from peristaltic constriction. The variable contour is evidence of normal wall flexibility. Peristaltic constrictions are usually short and relaxation of the wall is rapid. The average width of the jejunum is from about 2.5 to 3.0 cm. compared to a width of from 2 to 2.5 cm. for the ileal region.

The motility of the small intestine is greatly influenced by drugs and the kind of vehicle employed to suspend the barium sulfate. Glucose and fat mixtures may change the rate as well as the mucosal pattern. Motility is affected by buttermilk, malted milk and various flavoring extracts commonly used to make the barium mixture more palatable. Pendergrass and his associates have demonstrated these small bowel changes in motility and contour according to the kind of medium employed. They conclude from their observations that distilled water in combination with barium sulfate is the most satisfactory mixture because it eliminates any possible deleterious action from the presence of chlorine in ordinary tap water.

Alterations in the gastric emptying rate may likewise affect the motility rate of the small intestine. Motility may also be altered by varying degrees of hot and cold mixtures. Emotion and anxiety, as well as the degree and duration of the "fasting stomach," may affect the small intestine's motility to a very appreciable degree. Reflex characteristics from other pathologic conditions, particularly those of an intra-abdominal nature, may alter the motility rate of the small intestine.

The mucous membrane folds in the small intestine are known as the *valvulae conniventes*. They produce the characteristic mucosal pattern often referred to as the "herring bone" appearance seen in the x-ray film. These folds are usually from 1 to 2 mm. apart. In the lower segments of the jejunum the folds shorten and spread apart but do not become appreciably wider (Fig. 33).

Such a pattern is derived from the circular folds of Kerkring (valvulae conniventes) and from the secondary induced folds which may occur in the

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Such a pattern is derived from the circular folds of Kerkring (valvulae conniventes) and from the secondary induced folds which may occur in the

mucous membrane They are not obliterated by distention, and they persist in postmortem specimens They project into the lumen in a circular or *spiral form* During the passage of large boluses, the pattern may be obliterated except for circular folds near the periphery As the barium courses through the small intestine, a "feathery" or "snowflake" outline may evolve as a result of fragmentary loculations of small amounts of barium in the vasa digestiva



FIG 33 —A characteristic normal outline of the small intestine Typical herring bone contour The mucoasl folds are evenly balanced, the caliber is uniform

Varying regions may show concomitantly mucosal patterns coated in relief with barium sulfate-distilled water mixtures as "feathery," "flaky," "snowflake," "herringbone," and "stacked coin' outlines These appearances vary according to the composition of the food or barium suspension

medium, the rate of gastric emptying and the tonicity and motility of the intestinal tract, as well as other possible physiologic, chemical, and pathologic changes

Forssell[18] describes the mucous membrane relief as irregular disc like digestion chambers limited by simple transverse and diagonal folds They may be joined by a central connecting lumen or may be entirely closed off from one another They cause a roentgen picture like "rondeau of coins" or a coarsely feathered appearance of the intestine This type of relief appears throughout the small intestine Forssell also describes the longitudinal folds of the mucosa as the "barring pattern" which develops as a result of segmental contractions in the jejunum The outline of the small intestine changes in the ileal region where the contour of the loopings presents a smooth continuous column of barium which intermittently becomes segmented Compression or "spot" films of the terminal ileum may show a "stacked coin" outline and longitudinal folds may sometimes be demonstrated

The motor phenomena are combined effects of the muscularis mucosæ and the muscularis propria The mucosal folds change their form and direction With peristaltic activity they vary in width and height, they become obliterated in segmented areas and the progressive annular crescentic folds are converted into longitudinal folds according to the intensity of the motor activity

More recent physiologic research has shown that the muscularis mucosæ has an independent movement and reacts to mechanical and chemical stimuli in a manner similar to that of the muscularis propria It is this effect of the muscularis mucosæ which causes the progressive peristalsis of the valvulæ conniventes of the small intestine

Roentgenologic Abnormalities of the Small Intestine —The roentgenologic manifestations of a so-called "deficiency pattern" of the small intestine in nutritional disease are dependent upon the extent and duration of the disease and the degree of functional and morphologic alteration Abnormalities of contour and movement as revealed in films and fluoroscopic examinations at frequent intervals establish the basis for roentgenologic diagnosis A routine technical procedure is discussed in the paragraph on technique but this may be altered according to the individual case and the particular circumstances of the rate of motility

The roentgenologic criteria in nutritional diseases depend upon demonstration of distortions and abnormalities of contour in the small intestine and of abnormal rates of motility there The resulting complex, bizarre changes may be typical in one or all of a series of x-ray films obtained in a routine small intestine or progress-meal study Narrowing of the lumen segmentations jagged saw toothed and sometimes smooth rigid tubular outlines are typical roentgenologic changes Alterations of the mucosal folds coarsening irregularity, and obliteration are predominant effects that indicate undoubted abnormalities

The deficiency pattern is not always typical especially in the early cases Borderline evidence may become definite at a second examination In advanced cases the changes are usually marked and unmistakable

Roentgenologic manifestations of abnormalities of form and movement as shown in progress-meal studies in deficiency diseases have been classified by Golden[17–19] as follows

I *Motility*

1 Hypermotility
2 Hypertonicity
3 Hypomotility
4 Hypotonicity
5 Abnormal segmentations
6 Scattering effects—abnormal distribution of barium
7 Gas and fluid levels

II *Mucous Membrane Changes*



FIG 34 —Coarsening and irregularity of mucosal folds Marked hypertonicity

MOTILITY —*Hypermotility* —Hypermotility is variable in normal individuals The head of the barium column may reach the ileocecal juncture within from one and a half to five hours—on the average, within from two to four hours This hyperactivity *may be recognized in early stages of* nutritional disease



FIG 35 —Distortion and obliteration of mucosal pattern Narrowing of caliber and hypertonicity

Hypertonicity —Hypertonicity is usually manifested in the early stages of the disease These phenomena are not always easy to recognize unless they are marked They are relative in degree and are revealed by comparison with the alternating diminished and widened caliber of the bowel in scattered segments with intermittent distribution Even after peristaltic contraction there is not the usual relaxation, so that narrow, rigid, tubular

contours persist in different areas The lumen may be reduced to one half its normal width or less (Fig 35)

Hypomotility —Hypomotility is evident in the more advanced stages The barium may not reach the cecum for six or eight hours, and this is striking and significant evidence of dysfunction Mucosal changes are prominent and clearly shown There is usually a tendency to puddling and



Fig 36 —Hypomotility dilatation and segmentation Irregular, coarsened mucosal pattern

pouch-like dilatations of the small bowel loopings with barium, and the mucosal pattern tends to become coarsened, irregular, and obliterated These features are closely related to the dilated hypotonic contour (Fig 36)

Hypotonicity —Hypotonicity is manifested by a variable degree of dilatation The smooth-walled, ironed out contour with segmentations may present sausage-like configurations The obliteration of the mucosal folds

results in a "moulage" appearance (Kantor[20]), in contrast to the typical normal herring-bone contour These effects of pouchlike sacculations seem to be commensurate with the degree of delayed transit Any remaining mucosal folds are usually very irregular

Abnormal Segmentations —Abnormal segmentations are an effect of the rhythm and degree of peristaltic contracture or spasm These areas of constriction are variable and may be simulated by mechanical pressure and manipulation fluoroscopically The same individual may show marked difference at different periods of an examination on the same day and on different days (Fig 37)

Scattering Effects —Scattering effects of barium masses are the result of the degree of motility The flaky outline of clusters of barium and the herring-bone contour are commensurate with the degree of contracture and



Fig 37 —Hypotonic dilated segments Alternating coarsening and obliteration of the mucosal folds

rate of motility Delayed gastric emptying may accentuate or simulate abnormal appearances which must be considered with the detail of varying periods of the entire progress-meal study (Fig 31)

Gas and Fluid Levels —Gas and fluid levels are frequently encountered and may be present in considerable amounts The significance is not known, but Pendergrass suggests that gas may indicate a disturbance in the ability of the mucosa to absorb gas Small bowel gas should be considered abnormal and may be a factor of chemistry and fermentation under certain conditions In advanced cases, gas and fluid levels may simulate the appearance of ileus (Kantor [9])

MUCOUS MEMBRANE CHANGES —Mucous membrane changes may be very pronounced, especially in advanced stages Even in early deficiency states there may be definite detectable alterations of contour The folds may be unduly prominent, abnormally wide, and irregular in width, height, and spacing These changes result in a coarsening of the mucosal folds and vary according to the tone of contractures occurring with motility The normal herring-bone outline may be obliterated and replaced by a smooth, rigid tubular contour or occasionally redundant saccular formations

Changes in the small intestine are frequently not recognized in the early stages of deficiency disease Hypomotility of the stomach is commonly found in deficiency diseases Peristalsis may be shallow and gastric retention marked at six hours even in the absence of ulcer or obstruction Small bowel disturbances are most commonly found in the middle third region This area is also the last to clear up under treatment The terminal ileum rarely shows any demonstrable changes

With variation in the vehicle of the barium meal, the pattern and motility of the small bowel in normal individuals may suggest serious pathology, and the roentgenologist must be cognizant of these possibilities (Pendergrass[14])

The Roentgenologic Pattern in Infants and Children —The small bowel pattern in clinically healthy normal children presents such a varied pattern that a normal standard is very difficult to establish Abnormal calibers, dilatations, and segmentations considered abnormalities possibly related to nutritional disease in adults may be well within normal limits in children

Zwerling and Nelson[21] found wide variations in the small-intestinal pattern in a roentgenologic study of 77 presumably normal infants They have concluded that the roentgenologic appearance of the small intestine is not at the present time a reliable criterion for the diagnosis of nutritional deficiency states in children

Possible Mechanism of Abnormalities of Contour and Motility —Three kinds of movement are carried out by the small intestine—peristalsis, segmentation, and actual movement of the mucous membrane Fluoroscopically it may be possible to observe a pendulum-like effect and appearances simulating antiperistalsis as a result of the rapid peristaltic contractures

Segmentations are seen as multiple constrictions in transient ballooned areas of a bolus which separate and fuse in the process of propelling the barium column with peristaltic contractures

The rate of movement depends on the rate of gastric emptying, the kind and temperature of food, and emotional factors, as well as possibly related endocrine, chemical, and physiologic mechanisms not yet fully understood [8,9] Metabolic influences have not been sufficiently emphasized

Stimulation of the vagi increases tone and peristalsis, but stimulation of the sympathetic diminishes tone and peristalsis Peristalsis may occur independently of extrinsic nervous influences Peristalsis may continue normally for months after section of the vagi and destruction of the abdominal ganglia of the sympathetic (Wright[27]) Normal peristalsis is probably due to a series of coordinated local nervous reflexes in response to the chemical and mechanical stimulation set up by the food

The physiologic functions of the epithelium of the mucous membrane of the small intestine are very intricate Almost complete absorption of the products of digestion occurs in the small intestine The secretion is an alkaline fluid containing ferments fat, water and nitrogenous substances The chemical changes of absorption occur within the epithelial cells

Pathologic changes of edema round-cell infiltration, ulceration and fibrosis are undoubtedly important factors producing changes of contour Variation in bowel content undoubtedly influences the pattern to a definite degree, yet nonabsorbable hydrocarbons such as mineral oil produce a segmental distribution of the barium Excess fat in the form of cream combines with the barium mixture and results in a mottled, segmented arrhythmical contour very similar to the outline seen in sprue

The neurogenic theory of Golden[17] suggests that the small bowel changes are the result of damage to the plexuses resulting in (1) defective response of the circular and longitudinal muscles to the normal stimulus of intestinal content which produces changes in motility and tone as well as segmentation, and (2) defective function of the muscularis mucosæ resulting in changes in the mucosal folds

Hurst [3] elaborated a similar thesis for sprue and celiac disease, suggesting that the paralysis of the muscularis mucosæ results in a loss of the pumping action of the villi by means of which fat is conveyed in the large lacteals He suggests that there is a loss in the normal stimulation of Meissner's plexus In this way, the entire mechanism of the small-bowel pattern in deficiency states is related to the alteration in the nerve plexuses This hypothesis is based upon the following evidence (1) histologic evidence of damage to the intramural nerve cells in experimental and clinical advanced deficiency states (2) the importance of vitamin B in intracellular oxidation processes and therefore presumably in normal nerve function, (3) the small bowel pattern in infants, which closely resembles the "deficiency pattern and is thought to be due to incomplete development of the nervous system (4) the possibility that motor disturbances in the intestine may result from nerve impulses arising outside the intestinal wall (consider the effect of emotional disturbance on the small-bowel pattern), (5) the fact that pathologic changes in the intestinal wall following long-continued nutritional deficiency seem to vary widely in different individuals, whereas the damage to the intramural nervous system is thought to be uniform in all Reflex characteristics emotion anxiety and metabolic, constitutional, and allergic diseases are undoubtedly correlated with the nervous system

The mechanism that produces these varied changes in the small bowel pattern with reference to motility and caliber alterations is not readily explainable Reports lack much detail on the pathologic findings, and the available information, both experimental and clinical, is largely limited to advanced cases Little is known about the pathologic changes in early stages

Snell and Camp[5] suggest the possibility of "an inflammatory condition with edema of the mucosa and infiltration of the walls" Mackie and his collaborators,[7] in their study of sprue, mention, in addition to edema and infiltration, "a derangement of the motor function and variations in the muscular tone"

The demonstration of moderate edema in the intestinal wall by ordinary histologic methods is unreliable compared with tissue analyses for water and chloride content (Lepore and Golden[24]) Pathologic changes have been described in advanced human deficiency diseases such as sprue and beriberi as well as in experimental deficiency in animals

Atrophy of the tunica muscularis and of the mucosa, edema and round cell infiltration, fibrosis of the submucosa and ulceration have been described

A deficiency pattern was demonstrated in the presence of hookworm (*Necator americanus*) by Krause and Crilly[8] After anthelmintic therapy alone, there was a tendency to restoration of the normal pattern, though this was not complete in severe cases

Generalized amyloidosis, proved at autopsy, revealed roentgenologic evidence of widening, coarsening, and irregularity of the mucosal folds of the jejunum (Golden[18]) The occurrence of a deficiency pattern in acute granulomatous jejuno-ileitis was reported by Sussman and Wachtel There were no clinical or laboratory findings of nutritional deficiency This evidence indicates that the pattern can be produced by a process consisting of inflammation, edema, and thickening of the submucosa with acute ulcerations in the mucosa A possible complicating low-grade reaction to inflammation in the small intestine in nutritional disease may explain the altered small bowel pattern found in x-ray studies

ROENTGENOLOGIC TECHNIQUE

The small intestine is usually seen in a special gastrointestinal roentgen examination, in the course of which observations are made hourly or half hourly for from three to six hours after the administration of barium Combined film and fluoroscopic studies are essential Such a roentgenologic study is usually referred to as a "progress meal" or a "small intestine" study Variations in contour, motility, and mucosal patterns are depicted simultaneously, and alterations of a variable normal to abnormal degree may be correlated with the clinical and physical findings The routine gastrointestinal study generally shows the small intestine as well, of observations of the gastric emptying rate are made at two, four, or six hour intervals Very generally, when such routine observations are set for five or six hours, the outline of the barium will be largely in the terminal ileal region Very often if the emptying rate is unduly rapid, the duodenal and jejunal loop

ings are beautifully illustrated twenty or thirty minutes after the beginning of a fluoroscopic examination of the stomach

During the progress meal study, additional information may be obtained by the use of 'compression' or "spot" films of particular areas that show constriction or dilatation or delay of the barium column Such studies outline the mucosal pattern in striking detail and relief and are frequently of tremendous value in separating overlapping loops of the small bowel Sometimes the diagnostic evidence will be seen fluoroscopically by rotation and manipulation at only one of several observations and yet may not be conclusive in any one of half a dozen or more x ray films Frequently, with the patient in the erect posture, 'spot-compression films reveal circumstances not at all evident when the patient is prone or supine Satisfactory x ray films are best made routinely of the patient in the prone position The uniform pressure then serves to separate the overlapping loops and to some extent displaces to the midabdomen coils that otherwise might sag low in the pelvis An attempt was made to study the possible advantage of combining film studies in supine and erect postures with the routine prone position but the additional information was so slight that the use of these added positions did not seem to justify the extra time and expense

The exposure time must be short to eliminate the possibility of movement with consequent blurring of the outline and detail especially as a result of breathing aortic pulsations and vigorous peristaltic activity Excellent detail may be obtained with an exposure of only one or two tenths of a second Considerable improvement in quality and detail may be achieved if the available equipment permits the use of a fast Potter Bucky diaphragm

The gastrointestinal study should be begun with the patient on an empty stomach he should be made to fast for at least three hours and sometimes for six hours The head of the barium column may reach the ileocecal juncture within from one and a half to five or six hours—on the average, within from two to four hours Generally food will accelerate the motility rate, and this may result in misleading conclusions

When the roentgenologic evidence of a deficiency pattern is doubtful or even borderline, the examiner will wish to make further observations In such circumstances a second examination several days or a week later may reveal definite and unmistakable changes of a deficiency pattern

Sometimes there is an advantage in giving barium in small amounts—two or three ounces every ten fifteen, or thirty minutes—in order to stimulate motility and thus demonstrate alterations of contour to better advantage Prolonged observations are not always necessary The diagnosis may be evident as soon as the first loops of the jejunum are visualized

Hypervitaminosis may result from the administration of excessive amounts of vitamins A and D Prolonged and excessive amounts of vitamins A and D may result in roentgenologic changes in the bone structure that are very typical effects of an abnormal process [30–34] The roentgen changes represent appearances of a cortical hyperostosis These changes are not constant The most usual and characteristic features of cortical hyperostoses have not been present in all cases of excessive doses of vitamin A These roentgen changes have disappeared after withdrawal of vitamin A in controlled cases While there is evidence that large doses of vitamins A and D may be toxic and may result in hypercalcemia and resulting soft tissue calcifications and osteoporosis there is some question as to the mech-

anism of these effects It has been suggested that these changes may be related to the sterols rather than the toxic effect of the vitamins

These changes have been described in a newborn infant (Humbert), where the mother had consumed enormous amounts of commercial vitamin preparations and was given calcium injections during pregnancy

Hypovitaminemia B_1 may show alterations in the small bowel pattern, similar to the abnormalities seen in nutritional diseases [31] Interpretations of gastro-intestinal abnormalities and dysfunction must be considered with reservation because hypovitaminosis is by no means the only causative factor

SUMMARY

In this chapter, typical roentgenologic changes in bones have been briefly described for rickets, scurvy, and osteomalacia

A deficiency pattern may be demonstrated roentgenologically in a wide variety of pathologic entities and is not pathognomonic in deficiency diseases

The pathologic changes of edema, round cell infiltration, ulceration, and fibrosis are factors of great importance in producing the appearance described as a deficiency pattern Neurogenic, metabolic, chemical, and physiologic phenomena are likewise important

Atrophy of the mucosa may account for the roentgen appearance of coarsening or obliteration of the folds These changes are not easily explained The mucous membrane may be the origin of reflexes and the site of stimulating effects, and these responses may modify muscle contraction

Roentgenologic evidence of a deficiency pattern may not disappear even after there has been a decided clinical response to specific therapy

Technical improvements have permitted demonstration in greater detail of the mucous membrane outline Experiences have been accumulating and abundant *evidence is now available concerning the recognized criteria* of functional and structural effects of organic disease

Knowledge of the physiology of the small intestine is still limited, and many theories, as well as experimental data, need further investigation The processes of absorption and chemical change and the varied roentgenologic phenomena are complex, and their explanation will require much additional clinical and pathologic investigation

Roentgenologic interpretation of small bowel contours must be based on close observation of the variable outlines that may obtain in a large series of cases and on a systematic correlation with clinical findings, particularly the response to treatment of deficiency diseases Some knowledge of normal physiology and evidence of pathologic changes in the intestinal wall in deficiency states should be tabulated in its relation to roentgenologic findings suggestive of other pathology Early recognition of these conditions and their differentiation will depend upon such knowledge and experience

The final analysis will depend not only on the correlation of an immense amount of clinical data, but also on the careful summation of roentgenologic, anatomic and pathologic material

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The final analysis will depend not only on the correlation of an immense amount of clinical data, but also on the careful summation of roentgenologic, anatomic and pathologic material

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Part II Nutrition in Disease

Chapter 18

Criteria of an Adequate Diet

By Robert S Goodhart

Diet patterns and food habits vary not only from one nation to another, but also from individual to individual There is no single pattern of diet which must be followed to insure good nutrition No single food can be designated essential for life or health The animal body does require calories certain fatty acids, amino acids, vitamins, minerals and water in sufficient amounts and in proper combinations to permit optimal growth, maintenance and repair of tissues under the environmental conditions to which the particular individual is exposed The essential nutrients are widely dispersed in nature and can be obtained from many combinations of foods with varying ease Some people depend upon beef and pork as sources of amino acids, others prefer horse, fish, dogs, rats, snails, locusts, snakes, or venison These are all good sources of high quality protein

Not only do diet patterns and food values vary but so also do requirements for specific nutrients depending on genetic and environmental factors diet patterns severity and nature of stress situations age, sex, rate of growth, *etc* Largely because of these two factors—differences in nutritional needs of individuals and variation in nutritive value of foods—it is practically impossible to devise a general food plan that will be just right for everyone[1] There are other influences of major importance in determining the dietary requirements of either the individual or groups of persons These include the organism s ability to adapt to its diet to adjust to its environment, and the aspirations of the individual and of the society in which he lives It is not at all certain, for example that the nutritional requirements for maximal size early maturity, active sex life and maximal muscular development are identical with those for maximal longevity In fact there is considerable presumptive evidence to the contrary Diets designed to protect the individual against bacterial infections, *e g* tuberculosis may lower resistance to certain virus infections and predispose the individual to obesity and coronary artery disease in later years Thus statements such as "An adequate diet is one which meets in full all the nutritional needs of the person[2] have little meaning unless they can be interpreted in terms of either the person s ambitions for himself or the community s designs for or on him

The influence of social, political and economic considerations on nutrition teaching is nowhere more apparent than in the drafting of official or semi

official dietary standards for population groups. In Table 50 are compared the Recommended Dietary Allowances (revised 1958) of the National Research Council of the United States of America,[3] the Canadian dietary standards (approved December, 1948),[4] and the "Standard Nutritional Requirement for the Japanese" (approved by the Nutrition Council of Japan in 1954),[5] all for the young moderately active, adult male. While some of the differences, such as the facts that Canada's recommendations for vitamin A are given entirely in terms of carotene and that the Japanese apparently still subscribe to the idea that the protein requirement increases as energy expenditure increases[5] (not shown in Table 50), cannot be explained, the reasons for the major differences between the American, Canadian and Japanese standards cited rest in the milieu in which the standards were established and which determined the purposes for which they were drawn.

The Recommended Dietary Allowances of the Food and Nutrition Board, U.S.A. "are designed to maintain good nutrition in healthy persons in the United States under current conditions of living and to cover nearly all variations of requirements for nutrients in the population at large. They are meant to afford a margin of sufficiency above minimal requirements and are therefore planned to provide a buffer against the added needs of various stresses and to make possible other potential improvements of growth and function."[3]

The intent of the Canadian standard is quite different and involves the concept that "The ingestion of *more* of a nutrient than serves a clear physiological purpose is undesirable in the face of a world scarcity of food, and may even be harmful to the individual under certain circumstances."[4] "The standard is intended to be used (1) as a scientific basis for planning food supplies for individuals or groups except where clinical observations and tests have established particular food requirements, (2) to assess the amount of each nutrient provided by a diet in terms of probable physiological requirements, and (3) to indicate a "nutritional floor" beneath which the maintenance of health in people can not be assumed."[4] In regard to the degree of success achieved by the Canadian Council on Nutrition in descending to the "nutritional floor" for vitamin A, thiamine, iron (adult males) and ascorbic acid, the reader may care to refer to the chapters in this book where these nutrients are discussed in detail.

Again, the Japanese standard has still a different objective as indicated in the following quotations from a 1958 report of the Ministry of Health and Welfare on Nutrition in Japan.[5] "As a whole, therefore, nutrition of the nation is still more to be improved. It is not enough to meet all the requirements as the standard is based on the present physiques of the Japanese of today, and we are not satisfied to be in the present physiques, which are, compared to many other nations, rather dwarfish." "We are not satisfied, however, as we said before with just the recovery to the prewar state but aim to become one of the healthy, able-bodied and able-minded peoples of the world, and in a well grown size, too."

Since nutritional requirements vary, not only from person to person, but also in the same person since it is not possible to determine the precise requirements of any individual for many nutrients, and since the use of

TABLE 50 —U S A CANADIAN AND JAPANESE RECOMMENDED DIETARY ALLOWANCES FOR YOUNG MODERATELY ACTIVE MALE ADULTS

Standard	*Wgt in lbs*	*Calories*	*Protein gm*	*Calcium gm*	*Vitamin A I U*	*Iron mg*	*Thiamin mg*	*Riboflavin mg*	*Niacin mg*	*Ascorbic Acid mg*	*Vitamin D I U*
National Research Council U S A [a]	154	3200	70	0 8	5 000	10	1 6	1 8	21 (mg equiv)	75	0
Canadian Dietary Standard[4]	160	3000	70	0 75	5 300 *	6	0 9	1 5	9	30	0
Standard Nutritional Requirements for Japanese[a]	123 (56 kg)	2500	80	0 8	4 000	10	1 1	1 1	11	65	15

* Assuming two-thirds of the total vitamin A activity as carotene and one third as the preformed vitamin If the sole source were preformed vitamin A the allowance would be 3 000 I U

* Vitamin A given in terms of carotene If the source were preformed vitamin A, the standard would be 1 325 I U

TABLE 51 —CANADAIN DIETARY STANDARD FOR GIRLS AND BOYS 1948
(The figures in the table give the maintenance allowances for body weight shown plus additional needs for activity)

Body[1] Weight (lbs) with Approximate Equivalent Age in Brackets	*Calories*	*Protein gm*	*Calcium[2] gm*	*Iron mgm*	*Vitamin[3] A (as carotene) I U*	*Thiamine mgm*	*Riboflavin mgm*	*Niacin mgm*	*Ascorbic Acid (C) mgm*	*Vitamin D I U*
					GIRLS					
20 (1)	1 050	35	1 0	6	700	0 30	0 50	3 0	30	400–800
30 (3)	1 300	37	1 0	6	1,000	0 40	0 65	4 0	30	400
40 (5)	1,600	40	1 0	6	1,300	0 50	0 80	5 0	30	400
50 (7)	1,800	45	1 0	6	1 600	0 55	0 90	5 5	30	400
60 (9)	2,100	50	1 0	6	2,000	0 65	1 10	6 5	30	400
70 (10)	2 300	55	1 0	6	2,300	0 70	1 15	7 0	30	400
80 (11)	2,450	60	1 0	6	2,600	0 75	1 25	7 5	30	400
90 (12)	2,475	70	1 5	6	3 000	0 75	1 25	7 5	30	400
100 (14)[4]	2 500	75	1 5	12	3,300	0 75	1 25	7 5	30	400
					BOYS					
20 (1)	1 050	35	1 0	6	700	0 30	0 50	3 0	30	400–800
30 (3)	1,300	37	1 0	6	1 000	0 40	0 65	4 0	30	400
40 (5)	1,600	40	1 0	6	1,300	0 50	0 80	5 0	30	400
50 (7)	1,850	45	1 0	6	1 600	0 55	0 90	5 5	30	400
60 (9)	2,180	50	1 0	6	2 000	0 65	1 10	6 5	30	400
70 (10)	2,300	55	1 0	6	2 300	0 70	1 15	7 0	30	400
80 (12)	2,500	60	1 0	6	2 600	0 75	1 25	7 5	30	400
90 (13)	2 650	65	1 5	12	3 000	0 80	1 30	8 0	30	400
100 (14)	2 850	70	1 5	12	3 300	0 85	1 40	8 5	30	400
110 (15)[4]	3,000	80	1 5	12	3 600	0 90	1 50	9 0	30	400

1 Body weight or size is probably the most important cause of variations in nutrient requirements but is is recognized that other factors also operate and that not all of the nutrients listed have been shown to vary with body size
2 Calcium—use these values for phosphorus also
3 Vitamin A given in terms of carotene one-quarter of these amounts may be used if taken as preformed vitamin A
4 For children heavier than these weights use adult standards plus an allowance for activity

average requirements as a standard for diet planning and food production programs means, under any known system of food distribution and economics, that large numbers of people will fail to meet their nutritional requirements, the author subscribes to the approach taken by the National Research Council in establishing the Recommended Dietary Allowances as cited above. As a matter of information, the Canadian dietary standards (1948) are given in Tables 51 and 52. They will not be further discussed.

An adequate diet is considered by the author to be one which provides in sufficient amounts and with a reasonable margin of safety, all those nutrients required to permit the individual to realize his full physical, mental and emotional potential and which at the same time supplies a minimum of toxic or otherwise deleterious susbtances.

Calories.—The calorie used in the study of metabolism is the large calorie which is the amount of heat required to raise 1 kilogram of water from 15° to 16° C. Energy (calories) is required for all body processes and all of the individual's activities. The need is the sum of the basal metabolism + the energy liberated in exercise + the increment of energy due to the specific dynamic action of food. The two first are of determining influence, the third is of importance only when great precision in dietary arrangement is demanded.

Calorie standards have been published by the Food and Agricultural Organization of the United Nations.[6,7] The recommendations on calories contained in the 1958 revision of the Recommended Dietary Allowances (Table 53) represent a modification of the FAO standards made to conform more closely to the average sizes of young men and women in the United States and to our mean annual temperature. In the 1958 revision the "reference man," age 25, weighs 70 kilograms (FAO 65 kg.) and the "reference woman," age 25, weighs 58 kilograms (FAO—55 kg.). The mean annual temperature is taken as 20° C. (FAO—10°C.). These standard persons are presumed to be fairly active physically, being neither sedentary nor engaged in hard physical labor as a major occupation.[3]

In accord with FAO recommendations, the NRC suggests that calorie allowances be reduced by 3 per cent per decade between ages 30 and 50 and 7.5 per cent per decade from 50 to 70. A further decrement of 10 per cent is recommended for the years from 70 to 80.

For adjustment of calories for climate or seasonal differences, it is suggested that the allowance be increased by 5 per cent for the first 10° C. decrease from the standard of 20° C. and by 3 per cent for each additional 10° C. decrease. Allowances are reduced for high environmental temperatures by 5 per cent for each increase of 10° C. above the standard of 20° C. The National Research Council[3] also suggests adjustment for body size by the following formulae:

Calories for Men = 0.95 (815 + 36.6W*)

Calories for Women = 0.95 (580 + 31.1W*)

* W—desirable body weight in kilograms.

For all practical purposes in handling the individual adult patient, the author over a period of years has found it quite satisfactory to take the

TABLE 52 —CANADIAN DIETARY STANDARD FOR ADULTS, 1948

(The figures in the table give the maintenance allowance for the body weight shown plus additional needs for activity as indicated) [5]

Body[1] *Weight* (lbs)	*Degree of Activity*	*Calories*	*Protein* gm	*Calcium*[2] gm	*Iron* mgm	*Vitamin A*[3] (as carotene) I U	*Thiamine* mgm	*Riboflavin* mgm	*Niacin* mgm	*Ascorbic Acid (C)* mgm
			WOMEN						K	
80	Sedentary	1,625	40	0.40	12	2,600	0.15	0.8	4.5	30
	Moderate	1,900	40	0.40	12	2,600	0.55	0.9	5.5	30
	Heavy	2,400	40	0.40	12	2,600	0.70	1.2	7.0	30
100	Sedentary	1,825	50	0.45	12	3,200	0.55	0.9	5.5	30
	Moderate	2,100	50	0.45	12	3,200	0.65	1.0	6.5	30
	Heavy	2,600	50	0.45	12	3,200	0.80	1.3	8.0	30
120	Sedentary	2,125	55	0.55	12	4,000	0.65	1.0	6.5	30
	Moderate	2,400	55	0.55	12	4,000	0.75	1.1	7.5	30
	Heavy	2,900	55	0.55	12	4,000	0.90	1.4	9.0	30
140	Sedentary	2,325	60	0.65	12	4,600	0.70	1.1	7.0	30
	Moderate	2,600	60	0.65	12	4,600	0.80	1.2	8.0	30
	Heavy	3,100	60	0.65	12	4,600	0.95	1.5	9.5	30
160	Sedentary	2,525	70	0.75	12	5,300	0.75	1.2	7.5	30
	Moderate	2,800	70	0.75	12	5,300	1.85	1.3	8.5	30
	Heavy	3,300	70	0.75	12	5,300	1.00	1.6	10.0	30
In pregnancy[4] (latter half) add to the maintenance plus work		up to 500	25	1.0	3	2,000	0.15	0.2	1.5	
In lactation[4] add to the maintenance plus work		up to 1,000	25	1.0	3	2,000	0.30	0.5	3.0	

					MEN					
80	Sedentary	1 625	40	0 40	6	2 600	0 45	0 8	4 5	30
	Moderate	2 150	40	0 40	6	2 600	0 60	1 1	6 0	30
	Heavy	2 900	40	0 40	6	2 600	0 85	1 4	8 5	30
	Very Heavy	3 900	40	0 40	6	2 600	1 15	1 9	11 5	30
100	Sedentary	1 825	50	0 45	6	3,200	0 55	0 9	5 5	30
	Moderate	2 350	50	0 45	6	3,200	0 70	1 2	7 0	30
	Heavy	3 100	50	0 45	6	3 200	0 95	1 5	9 5	30
	Very heavy	4 100	50	0 45	6	32 00	1 25	2 0	12 5	30
120	Sedentary	2 125	55	0 55	6	4 000	0 65	1 0	6 5	30
	Moderate	2 650	55	0 55	6	4 000	0 80	1 3	8 0	30
	Heavy	3 400	55	0 55	6	4 000	1 05	1 6	10 5	30
	Very heavy	4 400	55	0 55	6	4 000	1 35	2 1	13 5	30
140	Sedentary	2 325	60	0 65	6	4 600	0 70	1 1	7 0	30
	Moderate	2 850	60	0 65	6	4 600	0 85	1 4	8 5	30
	Heavy	3 600	60	0 65	6	4 600	1 10	1 7	11 0	30
	Very heavy	4 600	60	0 65	6	4 600	1 40	2 2	14 0	30
160	Sedentary	2 525	70	0 75	6	5 300	0 75	1 2	7 5	30
	Moderate	3 050	70	0 75	6	5 300	0 90	1 5	9 0	30
	Heavy	3 800	70	0 75	6	5 300	1 15	1 8	11 5	30
	Very heavy	4 800	70	0 75	6	5 300	1 45	2 3	14 5	30
180	Sedentary	2 725	75	0 80	6	5 900	0 80	1 3	8 0	30
	Moderate	3 250	75	0 80	6	5 900	0 95	1 6	9 5	30
	Heavy	4 000	75	0 80	6	5 900	1 20	1 9	12 0	30
	Very heavy	5 000	75	0 80	6	5 900	1 50	2 4	15 0	30
200	Sedentary	2 925	80	0 90	6	6 600	0 85	1 4	8 5	30
	Moderate	3 450	80	0 90	6	6 600	1 00	1 7	10 0	30
	Heavy	4 200	80	0 90	6	6 600	1 25	2 0	12 5	30
	Very heavy	5 200	80	0 90	6	6 600	1 55	2 5	15 5	30

1 Body weight or size is probably the most important cause of variations in nutrient requirements, but it is recognized that other factors also operate and that not all of the nutrients listed have been shown to vary with body size
2 Calcium—use these values for phosphorus also
3 Vitamin A given in terms of carotene one-quarter of these amounts may be used if taken as preformed vitamin A
4 Vitamin D at least 400 international units is also needed

TABLE 53.—FOOD AND NUTRITION BOARD, NATIONAL RESEARCH COUNCIL RECOMMENDED DAILY DIETARY [illegible]
DESIGNED FOR THE MAINTENANCE OF GOOD NUTRITION OF HEALTHY PERSONS IN THE U.S.A.
(Allowances are intended for persons normally active in a temperate climate)

	Age Years	Weight kg (lb)	Height cm (in)	Calories	Protein gm	Calcium gm	Iron mg	Vitamin A I U	Thiamine mg	Riboflavin mg	Niacin[2] mg equiv	Ascorbic Acid mg	Vitamin D I U
Men	25	70 (154)	175 (69)	3200[3]	70	0.8	10	5000	1.6	1.8	21	75	
	45	70 (154)	175 (69)	3000	70	0.8	10	5000	1.5	1.8	20	75	
	65	70 (154)	175 (69)	2550	70	0.8	10	5000	1.3	1.8	18	75	
Women	25	58 (128)	163 (64)	2300	58	0.8	12	5000	1.2	1.5	17	70	
	45	58 (128)	163 (64)	2200	58	0.8	12	5000	1.1	1.5	17	70	
	65	58 (128)	163 (64)	1800	58	0.8	12	5000	1.0	1.5	17	70	
	Pregnant (second half)			+ 300	+20	1.5	15	6000	1.3	2.0	+ 3	100	400
	Lactating (850 ml daily)			+1000	+40	2.0	15	8000	1.7	2.5	+ 2	150	400
Infants[4]	0–1/12[4]				See								
	2/12–6/12	6 (13)	60 (24)	kg × 120	Footnote	0.6	5	1500	0.4	0.5	6	30	400
	7/12–12/12	9 (20)	70 (28)	kg × 100	4	0.8	7	1500	0.5	0.8	7	30	400
Children	1–3	12 (27)	87 (34)	1300	40	1.0	7	2000	0.7	1.0	8	35	400
	4–6	18 (40)	109 (43)	1700	50	1.0	8	2500	0.9	1.3	11	50	400
	7–9	27 (60)	129 (51)	2100	60	1.0	10	3500	1.1	1.5	14	60	400
	10–12	36 (79)	144 (57)	2500	70	1.2	12	4500	1.3	1.8	17	75	400
Boys	13–15	49 (108)	163 (64)	3100	85	1.4	15	5000	1.6	2.1	21	90	400
	16–19	63 (139)	175 (69)	3600	100	1.4	15	5000	1.8	2.5	25	100	400
Girls	13–15	49 (108)	160 (63)	2600	80	1.3	15	5000	1.3	2.0	17	80	400
	16–19	54 (120)	162 (64)	2400	75	1.3	15	5000	1.2	1.9	16	80	400

1 The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses

2 Niacin equivalents include dietary sources of the preformed vitamin and the precursor, tryptophan 60 milligrams tryptophan equals one milligram niacin

3 Calorie allowances apply to individuals usually engaged in moderate physical activity For office workers or others in sedentary occupations they are excessive Adjustments must be made for variations in body size age physical activity and environmental temperature

4 No allowances are stated for the first month of life Breast feeding is particularly indicated during the first month when infants show handicaps in homeostasis due to different rates of maturation of digestive excretory and endocrine functions Recommendations as listed pertain to nutrient intake as afforded by cow's milk formulas and supplementary foods given the infant when breast feeding [illegible] Allowances are not given for protein during infancy

calorie requirement of the average woman at 18 calories per pound of ideal body weight, and that of the average man at 21 calories per pound of ideal body weight with a range of from 15 for the very sedentary to 25 calories per pound for those habitually engaged in strenuous physical exertion On follow-up, indicated adjustments to meet actual individual requirements have proven to be relatively simple

Adjustments in caloric allowances are also necessary for pregnancy, lactation, growth, physical activity and metabolic aberrations To provide a table or formula by which these adjustments could be calculated with any degree of accuracy for the individual person would be to pretend to knowledge which we do not possess In the last analysis, calorie allowances must be adjusted to meet specific needs The proper allowance for an individual is that which over an extended period will maintain body weight or rate of growth at the level most conducive to well being [3] Height and weight tables are given in Chapter 1

Calorie allowances for infants and children are discussed in Chapter 35

Carbohydrates —There is no specific requirement for carbohydrates and there is no requirement for any specific carbohydrate In the United States carbohydrates provide from 40 to 50 per cent of the calories in the dietary Since carbohydrates provide a relatively cheap source of calories, the proportion is higher in the dietary of the lower economic groups than in that of the upper income brackets In general throughout the world the proportion of carbohydrate in the dietary appears to be determined by the availability or non availability of other foods Refined sucrose probably represents an exception to this rule since the consumption of this source of vitamin-free calories appears to be inordinately high wherever it is readily available

The more indigestible complex carbohydrates such as cellulose have an important function in providing bulk for the intestinal contents

Fats —Fats once valued chiefly for their high caloric value, are now assuming much greater nutritional importance The lack of certain fatty acids results in genuine nutritional deficiency a small amount of fat is therefore essential in man's diet At first this requirement was believed to be extremely small so small in fact as to be negligible but this is probably an error however it is not yet possible to state definitely a reasonable allowance for fat in the diet or to indicate the characteristics of a fatty acid mixture most favorable for the support of health beyond the general recommendation that prudence would seem to dictate a diet in which at least one half of the fat calories come from unhydrogenated vegetable oils (see Chapter 8) Approximately 40 per cent of the calories in the average American diet are provided by fat

Protein —The National Research Council[3] recommends a daily protein allowance for adults of 1 gram per kilogram of body weight The protein requirement is increased during pregnancy and lactation, and during recovery from disease and injury, but it is not increased by muscular activity, provided that the calorie requirement is satisfied Protein requirements are relatively high for the periods of rapid growth and lower during periods of slow growth It ranges from about 2 5 to 3 gm per kilogram of body weight in early childhood to 1 5 to 2 gm in late childhood and adolescence, to

approximately 1 gm. for adults.[8] The recommended allowances for protein assume adequate caloric intakes. For requirements during pregnancy and childhood see chapters 34 and 35.

Actually the requirement is for amino acids, rather than for protein as such, thus accounting for the higher biological value of animal proteins as compared to vegetable proteins, the latter being incomplete in amino acid composition for animal tissue synthesis. It is recommended that a variety of foods be included in the diet and especially foods of animal origin.

Vitamins.—The vitamins are organic substances required in minute amounts for the metabolism of foodstuffs and the discharge of important body functions. They are useless without substrata upon which to act or media in which to operate, without carbohydrates, protein, fat, water, oxygen and certain minerals. The proper foods are essential for health and the vitamins, either natural or synthetic, are essential for the efficient and optimal utilization of ingested foodstuffs by the body.

In Table 53 are listed the National Research Council's Recommended Dietary Allowances for vitamin A, thiamine, riboflavin, niacin, ascorbic acid, and vitamin D. It must be emphasized that these allowances are *designed for the maintenance of good nutrition of healthy persons in the United States of America*. Many healthy individuals require less than the recommended allowances and some apparently healthy persons require more. The Recommended Daily Dietary Allowances *do not* apply to persons suffering from disease, metabolic disorders and injury, and are *not* to be used as standards for hospital diets.

The vitamins listed in Table 53 are those about which sufficient is known to permit a reasonable degree of agreement on dietary allowances. They are also the vitamins deficiencies of which have been found to be most prevalent in the American dietary. Diets of customary foodstuffs adequate in these vitamins are not apt to be deficient in other vitamins *for healthy persons*.

Other vitamins known to be dietary essentials for man include vitamin B_6 (daily requirement for healthy adults probably around 1.5 mg.[8]), pantothenic acid (about 7 mg.[9]), folic acid (folacin) (1 to 2 mg.[8]), vitamin B_{12} (around 1 microgram[10]), choline (perhaps 150 to 250 mg.[9]), inositol (dependent on composition of diet and extent of intestinal synthesis[9]), biotin (perhaps 150 to 300 micrograms, considerable intestinal synthesis[10]) and vitamine E (around 7 mg.[8]). The requirement of healthy adults for vitamin K probably is around 1 mg. daily, probably met almost entirely, if not completely so, by intestinal synthesis.

Table 53 gives the niacin allowances in terms of niacin equivalents, or the total niacin available from the diet either as the preformed vitamin or as tryptophan. On the basis of work by Horwitt, Goldsmith and others[11] it has been calculated that 60 mg. of dietary tryptophan is approximately equivalent to 1 mg. of niacin. According to Horwitt[11] a diet which provides 60 grams of mixed protein provides approximately 600 mg. of tryptophan, or 10 niacin equivalents from tryptophan alone. "The niacin content, determined in milligrams by previously standardized procedures, is then added to give the total milligram equivalent to niacin."

Pharmaceutical vitamin preparations are of two general types, supple-

mental and therapeutic They may or may not include minerals, yeast and/or liver (as sources of unknown factors) and intrinsic factor to promote the absorption of vitamin B_{12} Supplemental vitamin preparations are intended for the correction of dietary inadequacies and the prevention of nutritional deficiencies They generally contain vitamin A, vitamin D, thiamine, riboflavin, niacin and ascorbic acid in amounts equal to or representing a substantial fraction of the Recommended Daily Dietary Allowances, when used as suggested by the manufacturer They generally *contain also forms of vitamin B_6, pantothenic acid, folic acid and vitamin* B_{12} Some polyvitamin preparations include, in addition, the other vitamins mentioned above as dietary essentials

Supplemental vitamin preparations often are suitable for the treatment of deficiency states in infants and young children but they are not intended to be used to correct such states in older children and adults For this purpose therapeutic vitamin preparations containing much larger quantities of the vitamins per recommended dose, are available Vitamins intended for therapuetic purposes are supplied in various combinations and singly to permit the most efficient use by the physician in the management of deficiency states which may be primarily of dietary origin or secondary to other disease states or metabolic aberrations Therapeutic polyvitamin preparations *are indicated for the correction of tissue deficits* resulting from dietary inadequacy, even though functional or anatomic evidences of vitamin deficiency may not be demonstrable This is in contradistinction to the use of supplemental vitamins for the prevention of dietary inadequacy

Minerals —*In selecting diets, calcium phosphorus, iron and iodine* are the minerals requiring most consideration Calcium and phosphorus are the minerals required in largest amounts The phosphorus allowances should be at least equal to those for calcium (Table 18) in the diets of children and of women during the latter part of pregnancy and during lactation For other adults, the phosphorus allowances should be approximately one and one half times those for calcium Generally, if the calcium and protein *needs are met through common foods the phosphorus requirements also* will be met

In the absence of growth pregnancy or blood loss the iron requirement is readily met by the customary mixed diet however during the period of active growth and during the active sexual period of the female special attention must be given to the iron content of the diet and supplementary iron may be indicated, iron deficiency anemia is common (See Chapter 10)

The requirement for iodine is small probably about 0 002 to 0 004 mg per day per kilogram of body weight [3] or a total of 0 15 to 0 30 mg daily for the adult This *need can* be met by the regular use of iodized salt During adolescence and pregnancy it is of special importance that an adequate intake of iodine be assured

Potassium is especially abundant in both plant and animal tissues and does not need particular consideration The average intake of sodium chloride (salt) by the normal adult is 7 to 15 gm daily This includes sodium and chlorides contained in foods as well as those added to food as salt It more than meets the normal requirements Under unusual con-

ditions, such as doing heavy work in a hot climate, 10 to 15 gm daily, or even more, may be required with meals and in drinking water However, after acclimatization to heat the sodium content of sweat is greatly reduced and the allowance for salt can be near to normal

It has been estimated that a young child requires about 13 milligrams of magnesium per kilogram of weight to satisfy growth needs, and the adult requirement has been estimated at 250 to 300 milligrams daily A mixed diet of plant and animal food provides from 250 to 300 milligrams per day [3] (*Also see* Chapter 9)

The requirement for copper by adults is about 2 mg daily Infants and children require approximately 0 05 mg for each kilogram of body weight The requirement for copper is approximately one-tenth that for iron A good diet normally will supply sufficient copper

Certain trace elements, in addition to copper and iodine, commonly found qualitatively in biological organisms have functional significance most frequently associated with enzyme systems Other than that the amounts are exceedingly small, relatively little is known about the quantitative levels necessary for essential physiological function of these elements in human nutrition, and less is known about desirable levels Included are manganese, molybdenum, and zinc

Water —A suitable allowance of water for adults is 2 5 L daily in most instances An ordinary standard is 1 ml for each calorie of food Much of this quantity is contained in prepared foods Water should be allowed *ad libitum* Sensations of thirst usually serve as adequate guides to intake, except for infants and sick persons Under conditions of extreme heat or excessive sweating, the sensation of thirst may not keep pace with the actual water requirements, and forced intakes up to 1 L per hour may be indicated for a short time [3]

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Chapter 19

A Nutrition and Natural Resistance to Infection

By Theodore F Zucker

Before taking up the evidence concerning relations between nutrition and natural resistance to microbial infectious states, it is advisable to consider the framework within which a satisfactory discussion can take place

The terms natural resistance and natural immunity are used to designate an innate state in which the host resists damage by a microbial invader even if the organism is present on the surface or in the tissues Various phases of the situation where a microbe will live or even propagate in or on host tissues without causing pathological change have recently been extensively discussed by Dubos[1] Such innate resistance of the host is genetically determined In contrast to acquired immunity it is not dependent on previous experience of the host with the invader Acquired immunity has apparently received more attention than the native resistant state both because on its basis a highly developed scientific discipline has evolved—immunology—and because artificial immunisation has, in cases where it is effective yielded results of immeasurable practical value in man and other animals However, as Raffel[2] (p 3) states The native defenses are of tremendous importance to daily welfare of the body—much more so than the specifically acquired properties The genetic control of natural resistance needs to be borne in mind at all times since it has a direct bearing on the observations recorded in the field of nutritional effects on resistance

It is well known that resistance—or conversely susceptibility—to microbial disease is frequently a property (either absolute or relative) of an animal species Zinsser[3] has listed some of the outstanding pertinent observations

Within a species there are also individual or strain differences This is illustrated abundantly by the studies of Webster Gowen Schneider and others By selection from a common stock strains have been bred one of which is highly resistant to a given infection and another is highly susceptible Such heightened susceptibility or resistance is then an innate property of the new selected strains and is passed on to successive generations When resistance to a given microbe was thus established, this could still leave the animals highly susceptible to other infective agents For instance, Webster[4] had four mouse strains one of which was susceptible to both mouse typhoid and an encephalitis virus a second strain was resistant to both agents the third and fourth strains were susceptible respectively to one but not the other agent Such a condition is understandable only

if there are separate mechanisms, genetically controlled, which ward off the attacks of each of the several invaders.

As we will illustrate later, we cannot expect that a given nutritional improvement should protect against any variety of infective agent, nor can we expect a nutritional factor which appears to affect resistance in one strain or species of host to do so necessarily in another.

MECHANISMS OF NATURAL RESISTANCE

If we are to comprehend how nutrition could influence natural resistance, we must consider what is known concerning the various barriers or defense mechanisms which protect the host against microbial disease. We will here briefly review what has been given in greater detail by Raffel,[2] by Dubos[1] and by Nungester.[5]

Epithelial surfaces—skin and mucus membranes—are physical barriers to penetration by microorganisms. Protection depends not only upon the intactness of the epithelial covering but there are also effective adjuvant mechanisms. Cilia in the respiratory apparatus help to repel and expel the invaders. On the skin fatty acids and soaps have been shown to exert considerable germicidal action.

Naturally occurring bactericidal substances in tissues and body fluids have been discussed in the literature from the early days of bacteriology. In the serum von Behring many years ago described a substance called beta lysin which was active against a variety, but not all, of the organisms tested. (Alpha lysin was the name for an immune antibody.) Comparing beta lysin from various animal species a certain selectivity was found as to the organisms on which it can act. Its existence is generally accepted, although its nature has not been determined. Its action is assumed by some to be enzymic.

Metchnikoff dealt with leukin, a bactericidal agent in serum which was derived from leukocytes. To this was added later a substance called plakin, derived from blood platelets. Saliva, nasal secretions and tears contain agents which will kill certain types of bacteria or viruses. Lipid fractions have been obtained from serum which show antibacterial or antiviral activity.

With regard to a number of such agents, their activity is known but practically no data are available as to their nature or chemical composition. More recently several substances have come to the fore which can be chemically characterized and whose activity is also more definitely circumscribed.

Lysozyme was first described by Fleming[6] as occurring in various mucous secretions. In man it is particularly abundant in tears. It also occurs in egg white. From the latter source it has been isolated in crystalline form. It is a basic low molecular weight protein (circa 17,500). Its salient property is that of an enzyme which will lyse or otherwise inactivate certain bacteria by acting on polysaccharide components of the membrane. Its action was at first thought to be restricted essentially to Micrococcus *lysodeikticus* but it is now known to act also on other bacteria.

Bloom and associates[7] have isolated from tissues of animals naturally

resistant to anthrax infection, a polypeptide with a high lysine content among its component amino acids This polypeptide kills anthrax bacilli *in vitro* and, when injected into mice, acts as an antibiotic Its action is not limited to Bac *anthracis* The findings of this group of investigators have contributed much new information on the involved relation of this organism to the host including phases of both natural resistance and acquired immunity

Several recent paths of investigation have led to substances which assist the bactericidal activity of host serum Among these are the properdin of Pillemer[8] and the lipopolysaccharide fractions studied by Rowley[9] and by Landy[10] The reactions do not lead to immune antibody formation and they are not specific, but do involve a response to fractions of bacterial or other cells They are a phase of natural defense and are so treated in a symposium on 'Natural Resistance to Infection' to which the citations refer

Phagocytosis by the blood leukocytes or by macrophages of the reticulo endothelial system is among the most potent defense mechanisms Success ful activity of phagocytes involves several phases namely, wandering of circulating phagocytes to the site of infection stimulation and proliferation of reticulo-endothelial macrophages in situ ingestion of the microorganism, and its destruction within the phagocytic cell Recent investigations of factors which affect these activities are of interest since they contribute biochemical data to possible mechanisms Tullis and Surgenor[11] have studied factors in serum which stimulate phagocytosis by circulating phagocytes They have characterized two proteins of such activity by physical and chemical methods These are not identical with complement or with opsonin and are apparently also distinct from Pillemer s properdin[8] The materials were derived from the blood of healthy donors There is evidence that the substances are not immune antibodies some of which can also stimulate phagocytosis *

Hirsch[12] has studied the bactericidal power of leukocytes Some of it is due to acid formation and to lysozyme but he also found a globulin which differs from heretofore described bactericidal agents It acts on gram negative bacteria is found in the polymorphonuclear leukocytes of man, rabbit and guinea pig but not in those of the rat and mouse

If an infective agent has passed epithelial barriers it generally sets up the chain of processes called *inflammation* which is in part a protective mechanism overlapping with or embodying those previously mentioned Its contributions to resistance are of several kinds Blood leukocytes are attracted to the site (chemotaxis) and formation of fibrin assists the phago cytosis and also helps to localize the invader mechanically Exudation of

*A passage of interest in this article may be quoted (p 386) The presence of such phagocytosis stimulating substances is not a new finding In fact the literature in this field dates back more than half a century Unfortunately, however this literature sometimes has been enmeshed in semantics should such factors be called opsonins? should such factors be called alexin? Or indeed are such factors merely manifestations of complement activity? For purpo es of simplification we have grouped all the protein factors that stimulate natural nonimmune phagocyto is under the descriptive term of phagocytosis promoting factors or PPF Points at which such activity varies from the classic concepts of complement and opsonin will be amplified

plasma may supply increased amounts of antibacterial substances and dilute or remove toxic products The local rise in temperature which accompanies inflammation may lessen the proliferation of some microbes

Other mechanisms are known which apply to particular invader or host species Among these a totally unexplained indifference of tissues to bacterial toxins may be mentioned For instance a rat will tolerate 1000 times the dose of diphtheria toxin that is the minimum lethal dose for the guinea pig A possible analog to this situation may be found in some observations of Hill, Hatswell and Topley[13] They selected for high resistance to the endotoxin of S *typhimurium* in ten successive generations of mice Compared with controls, the mice acquired a great tolerance or indifference to the toxin Since transmission of passive immunity was excluded in their technique, the result was an example of natural resistance intensified by selection In this case, however, resistance to the toxin did not confer resistance to inoculation with the live organism

Among environmental factors which predispose to infection are exposure to low temperatures and fatigue (see Topley and Wilson[14]) The environmental factors have more recently been partly reformulated under the head of "stress" and corticoadrenal activity

In this chapter we will not try to cover the literature on our topic This has been done at intervals (Clausen,[15] Robertson,[16] Schneider,[17] Raffel,[2] pp 173–183, Clark[18]) with varying critical analysis of the data Some of the contributions in the past have little value because they were carried out before sufficient knowledge of the factors concerned was available, and some may have to be classed as imperfect experiments On the other hand papers which have received little attention turn out to contain valuable sound data Our plan is to present certain topics which help to understand the subject as a whole

NUTRITIONAL EFFECTS ON NATURAL RESISTANCE

Just as exposure, fatigue, etc do not indiscriminately lower bodily resistance, so also we must not expect nutritional effects, if present, to be of a universal nature When we consider the variety of host species we are interested in (man, domestic animals, laboratory animals), the vast number of potential invaders, and the variety of protective mechanisms to be dealt with, we can readily see that we have no general information from which *a priori* deductions can be made With our present knowledge we need to consider closely specified cases

To emphasize the uselessness of generalisation, we should from the start realize the converse of what might be expected, namely, that nutritional deficiencies can also exert a protective effect on the host Probably the first indication of poor nourishment favoring resistance is the observation of Rous[19] that healthy well nourished chicks were more susceptible to the fowl sarcoma virus than those which were undernourished Similar results with fasting and fed rabbits in relation to vaccinia virus were reported by Sprunt[20] Going from rather undefined manition to particular single deficiencies, we can now consider some experimental results which illustrate various phases of the relation of nutrition to natural resistance Con

tinuing for a moment the consideration of viruses it is now definitely established that in a number of cases deficiency of particular nutritional essentials may increase natural resistance [1] This phenomenon of increased natural resistance due to a deficiency is not limited to viruses According to Seeler and Ott,[22] riboflavin deficiency in chickens increases resistance to Plasmodium *lophuræ* an organism of avian malaria

Animal Experiments Suggested by Experience with Human Infections

Malaria —Let us hark back to what has been said above concerning breakdown of resistance by environmental factors Williams [3] on the basis of wide experience with malaria in children in and about Singapore states " presence of malaria parasite in the blood of children apparently normal and healthy in every way One must consider these individuals as living in temporary symbiosis with the parasites They are apt to develop an attack of fever if subjected to chill overwork underfeeding or any particular strain"

As an experimental model to test nutritional effects avian malaria was used The experimental animals were ducks and chickens The organisms were Plasmodium *lophuræ* or P *cathemerium* The first successful lowering of resistance was obtained in ducks which were made deficient in biotin by feeding a diet high in raw egg white (avidin) (Trager [4]) Later experiments were carried out with biotin deficient diets The lowered resistance, measured by the count of parasites per 10 000 red blood cells, was observed before any outward signs of deficiency were apparent The particular role of biotin was verified in chicks by Seeler, Ott and Gundel,[25] who also found that riboflavin deficiency appears to increase resistance The observations of Roos Hegstedt and Stare [6] on chicks showed that deficiency of thiamine had no effect, that of choline a questionable one While niacin deficiency lessened the resistance, vitamin A deficiency appeared to increase resistance

Typhus —Zinsser *et al* [27] found that with rather poorly defined diets guinea pigs deficient in ascorbic acid and rats deficient in B complex showed an increased susceptibility to rickettsial infection Pinkerton and Bessey [8] were able to show that riboflavin deficiency in rats had a similar effect They also recorded a rapid response to administration of riboflavin even in almost moribund animals Zinsser, on the basis of his wide experience with typhus, suspected that nutritional deficiencies might have an effect, but the objective of both his work and that of Pinkerton and Bessey was to obtain a larger yield of rickettsial bodies for further study

Fitzpatrick s studies[29] were motivated by reports "that there is an increased mortality in epidemic typhus when the disease manifests itself in malnourished populations" Realizing as did Zinsser, that, in regions of disaster or malnutrition for any reason, nutritional deficiencies were only one of the factors which might be responsible for exacerbated typhus she undertook to ascertain to what extent various deficiencies could be shown to have an effect in animal experiments She made her observations not on total deficiency of any one factor but rather with partial deficiencies which more nearly resemble conditions to which man might be subjected Reducing the levels of the vitamin B factors to one-tenth of the usually

assumed requirement for the rat, she found that pyridoxine, niacin, choline and p-aminobenzoic acid did not modify resistance, while deficiency of riboflavin, thiamine and of pantothenic acid lowered resistance. Purified casein sugar diets with all essential factors available at the time led to more susceptibility than a stock diet of natural foods, thus indicating that unknown factors might have activity. Addition of liver powder having no effect showed that what were later designated as B_{12} and folic acid were not concerned. There was a possible minor role for protein deficiency.

We have here two instances where on clinical or epidemiological grounds nutritional effects on the course of the disease were envisaged. In both cases experimental models showed that certain deficiencies had an effect and others did not. The fact that more than one kind of deficient diet lowers defense barriers raises the question whether more than one type of defense mechanism comes into play or whether the same defense mechanism may be affected by several different deficiencies. The animal experiments make it plausible that the course of malaria and of typhus in man is affected by nutritional deficiencies but whether in man the same mechanisms are in control as in the pertinent animal species is still an open question.

Secondary Infections

It is easily understood that intact epithelial surfaces and adjunctive protective mechanisms can form effective barriers to infection. It is also known that some nutritional factors are essential for intactness of such surfaces. In niacin deficiency of both dogs and man there are marked atrophic and inflammatory changes in the oral mucosa. At such sites accumulations of various microorganisms occur. In riboflavin deficiency cheilotic lesions may become infected with staphylococci and hemolytic streptococci. Such infections yield readily to treatment with riboflavin.[30] In these cases infection when it occurs in tissues is looked upon as secondary to pathological change which is a consequence of the deficiency.

A much more important manifestation of such secondary infections may be found in the eye in vitamin A deficiency. Xerophthalmia, keratomalacia and resulting blindness have been known in man for nearly a century. As to cause there were many implausible speculations. Until the time when these signs were recognized in rats as a result of experimental vitamin A deficiency[31] the prognosis was poor with high mortality. To the pioneer work of the Danish investigator Bloch (first published in 1917) we owe the first sound demonstration that keratomalacia in man is due to vitamin A deficiency. A summarizing report on keratomalacia in Denmark was published by Blegvad.[3] A lengthy paper by Sweet and K'ang[33] reviews the observations of various workers at the Peiping Union Medical College. Both these papers have excellent bibliographies also covering the older literature. From these reports it appears that, in China and under conditions of excess export of butter fat in Denmark, vitamin A deficiency led to much xerophthalmia and keratomalacia. Blegvad reported that, out of 391 cases where information on the eyes was available, 93 succumbed to the disease (cause of death usually a bronchopneumonia), 27 per cent were blind and 24 per cent had vision greatly reduced in one eye. Sweet and

Kang state that *among autopsy cases lesions of the eye were the most* frequent Edema and necrosis were followed eventually by ulceration and secondary bacterial infection Perforation of the ulcer opened the way for panophthalmitis and permanent blindness When treatment with vitamin A was given before perforation took place the ulceration could heal and eyesight was saved

Not only can secondary infections following inadequate vitamin A intake have very serious consequences in man but the same applies to experimental animals Stoerk and associates[4] state that 'metaplasia of the corneal epithelium almost invariably led to keratitis iritis and even complete destruction of the eye Tracheitis pyelitis cystitis and endometritis were found in association with squamous cell metaplasia of the *respective epithelium so that in many instances the infection was obviously* related to inadequate protection afforded by defective lining' To obtain evidence concerning cause of death in vitamin A deficiency they gave daily injections of a penicillin streptomycin mixture 'In view of the improvement of growth and survival brought about in the vitamin A deprived animals by penicillin streptomycin treatment the possibility that secondary infection is one of the main causes of death of vitamin A deficient rats seems strongly supported

The space given to the above account of well known facts concerning vitamin A has the purpose of pointing out that the secondary nature of infections due to primary morphological changes does not lessen their importance The initial real cause is a nutritional deficiency and prevention depends on good nutrition The fact for instance that signs of vitamin A deficiency are rare in this country (Follis[35]) should not detract from our interest in the natural history of keratomalacia It simply means that as far as vitamin A is concerned we are well off

The apparent hesitation of some writers to discuss this role of vitamin A seems referable to two quite understandable circumstances In the course of development of knowledge concerning this factor some investigators on the basis of inadequate data desired to consider vitamin A an anti infective vitamin' irrespective of the cause or type of infection Obviously it will prevent or ameliorate infective states only if these are referable to a vitamin A deficiency A further discouragement came through Wolbach s observation[36] on what had been called sublingual abscess in vitamin A deficient rats This readily observable lesion with very high incidence had erroneously been taken *for an incontrovertible sign of infection until* it was shown to be not a pus containing abscess but a cyst filled with desquamated epithelial cells and other detritus resulting from the disorganizing effect of vitamin A deficiency (The cited reference to Wolbach contains a full and excellent discussion of the whole pathology of vitamin A deficiency)

Much pointless discussion has arisen from the earlier insistence that susceptibility to infection should be indicated by one or the other of the immunological criteria of loss of humoral defenses However as early as 1924 Cramer and Kingsbury[37] in a paper on infections associated with vitamin A deficiency in rats said In addition to the general humoral defenses against infection there are local defenses for certain organs such

as the intestines, the eyes and the lungs A diet deficient in vitamin A impairs the efficiency *of the local defenses It does not* appreciably diminish the efficiency of the general humoral defenses The study of these agencies emphasizes the importance of the local defenses by showing that their breaking down will allow infections to set in even though general defenses remain unimpaired" We can understand why Miles[38] should say "Antibody has dominated the study of resistance for the last 70 years sometimes to the detriment of research into natural resistance"

Effect of a Deficiency Varies with Host Species

Since the natural barriers to infection vary from species to species it would be surprising if a nutritional defect which lowers resistance to a given invader in one host species should necessarily do so in another host species

An interesting example may be seen in work with pneumococcus type I in mice and in rats Woolley and Sebrell[39] with groups of 50 mice each, found that on purified diets with either lowered thiamin or lowered riboflavin (0 5 gamma per gram of diet) the resistance was lowered, as measured by mortality Robinson and Siegel[40] carried out observations in rats on purified diets deficient in thiamin, riboflavin, pyridoxin or pantothenic acid, compared with controls on a complete purified diet and a natural food stock diet Two additional groups had restricted intake of the complete purified diet resulting respectively in mild and severe inanition Results in groups of 19 or 20 rats were judged by percentage mortality and survival time Among the purified diets, only that deficient in thiamin showed a marked lowering of resistance, with a possible effect from pyridoxin deficiency Riboflavin or pantothenic acid deficient diets as well as mild or severe inanition had effects no different from the complete purified diet A rather unexpected result recorded in these rat studies of Robinson and Siegel was a lower resistance to pneumococci on the stock diet of natural foodstuffs than on the purified diet

This may be the occasion for consideration of suitability of control diets Hitchings and Falco[41] recorded similar but much larger differences in mice when they compared a purified complete diet with three different crude stock diets including that of Robinson and Siegel They administered the pneumococcus type I by intraperitoneal injection In a paper[4] based on comparison of whole wheat and white bread they found the latter conferring more resistance and cite these results as "an example of a better diet being more favorable to the parasitic organism than to the host" What is a "better diet?" We know of diets that are better for growth than others, or for life span It is however very problematic whether any single diet fed exclusively has been found which is "better" for all purposes that a diet may serve It may be that the stock diet contains some substance whose presence lowers resistance, but the possibility is not excluded that the well supplemented purified diet contains more of a particular protective factor than the stock diet Dubos[43] also records experiments in which a commercial stock diet fed to mice led to less resistance to experimental tuberculosis than a well planned purified diet He makes no assumptions regarding high quality of natural food diets but raises questions with

regard to suitability of current stock diets—*e g*, the fact that while adequate in total protein plant proteins of low quality are present rather prominently In contrast to the results just mentioned we may note that in typhus work on rats Fitzpatrick[29] found a natural food stock diet more favorable to resistance than the purified diet More information on the exact properties of crude stock diets seems very desirable The term adequate or good stock diet has little meaning unless data are available as to purpose or function for which it is good

Loss of a Species Characteristic Resistance

Corynebacterium *Kutscheri* is the cause of a well known respiratory disease in mice This organism is generally held to be non pathogenic for rats A loss of this species characteristic in rats was shown by Gundel Gyorgi and Pagel[44] in early experiments with deficiency of vitamin H (biotin) The deficient rats developed a disease picture closely resembling that in mice Zucker and associates[45] have studied a similar situation in pantothenate deficient rats In these experiments the pantothenate deficient rats showed the species susceptibility characteristic of mice Young animals on pantothenate deficiency spontaneously developed lesions in the chest cavity in 7 to 9 weeks from which pure cultures of C *Kutscheri* could be isolated (Seronde[46]) In other deficient animals cultures were inoculated intraperitoneally This was followed by abscesses on peritoneal surfaces which later were seen to spread to the chest cavity resembling the spontaneous lesions (Seronde *et al* [47]) The animals were subject to successful inoculation even while still growing It is interesting to note that this same spontaneous disease turned up in rats receiving massive doses of cortisone (LeMaistre and Thompsett[48])

Multiplicity of Mechanisms in Resistance to the Same Invader

In pantothenate deficiency ulceration and necrosis in the mouth (first described by Wainwright and Nelson[49]) has been found by Seronde[46] to be at times very extensive together with involvement of the cervical lymph nodes This suggests the site of breakdown of resistance so far as the spontaneous lesions in the chest cavity are concerned Other mechanisms must be active when on intraperitoneal injection of a culture the high resistance of the well fed rat is turned into marked susceptibility A further indication of multiple mechanisms is found in the fact that deficiencies of pyridoxin and (partially) of thiamine had no effect on the spontaneous disease while they led to some reduction in resistance to intraperitoneal injection [50]

In vitamin A deficiency metaplastic changes in surface epithelium are put forward as an initial step in secondary infection Boynton and Bradford[51] have reported on intraperitoneal injection of an organism derived from naturally infected respiratory passages of rats (mucosus capsulatus group) Survival time of the deficient rats was much shortened At autopsy acute purulent peritonitis characterized the deficient animals Lungs kidneys spleen and liver also showed evidence of acute infection

Pure cultures of the organism were recovered from heart blood The dose of organism chosen was such that normal rats of similar weight just survived Particularly noteworthy is the fact that the lesions occurred far removed from the type of epithelium which is structurally altered by A deficiency It therefore appears that resistance in A deficiency may be lowered by a mechanism which does not involve epithelial changes The authors noted that the loss of resistance preceded the appearance of any overt signs of deficiency

Interaction of the Genetics of the Pathogen with Nutritional Effects

Few nutritional effects on resistance have been as well established with all necessary controls and many replications as in the case of salmonella infection in mice The first of a series of papers from Webster's laboratory at the Rockefeller Institute was published in 1924 The work of Webster and associates together with that of British investigators has been critically reviewed by Howie[53] It *appeared* that a factor responsible for increased resistance is contained in wheat Schneider in Webster's laboratory undertook isolation studies It was an arduous task with time consuming assay technique In 1956 he (Schneider[54]) could report an overall concentration of the factor of a millionfold, with efficiency of about 20 per cent He also described a shortened assay technique and outlined the processes involved in concentrating the substance The chemical nature of the material is still unknown There is no storage of this factor, one day on either the protective or non-protective regime leads to essentially the same results as longer periods

Another side of Schneider's work requires attention He expresses a point of view with regard to the nature of innate resistance which is contrary to generally accepted teaching In a speculative course of reasoning he maintains that resistance depends on and is revealed only by an interaction between more virulent and less virulent organisms present in the inoculum, and is not due to the activity of, or any force within, the host He operates with a highly virulent and an avirulent culture of *S typhimurium* and mixed virulent and avirulent cultures He also uses mice of three kinds Two of these are Webster's inbred relatively resistant and relatively susceptible strains The third is the original Webster Swiss mouse consistently outbred so that the animals show a range of resistance Now it is granted that a culture can be virulent enough to give 100 per cent mortality even with relatively resistant mice, and also virulence can be so low that even susceptible animals all survive This does not reflect on the nature of resistance—we know there are degrees From the fact that with mixed virulent and avirulent cultures, and the outbred mice, evidence of the existence of a nutritional effect on natural resistance is found, he infers that interaction between cells of different virulence is the basis for natural resistance and that this is not due to action on the part of the host However it is known that the principal defence of the mouse against *S typhimurium* (Oerskov[55]) and similar salmonellas is through phagocytosis and killing of the organisms by the macrophages of the reticulo-endothelial system, and Oakberg[56] has shown that the difference in resistance of mouse

strains depends on differing abilities of the macrophages to deal successfully with the invader Oerskov made observations on salmonella types of differing virulence and it is apparent that the fate of the animal or the number of viable organisms which remain depend on the balance between the virulence of the pathogen and the ability of the reticulo endothelial system to kill the invader In Webster s original experiments[5] no unusually virulent clonal cultures were employed such as Schneider used and the efficiency of the reticulo endothelial system was sufficient to allow a range of resistance to be shown by the heterogeneous mouse population he used These conditions allowed the effect of the anti salmonella wheat factor to become evident

Schneider says[57] ' Natural resistance though it is an attribute of the host is not to be conceived as a barrier an antibiotic or an opposed force Oakberg s experiments show an opposed force which protects the resistant mouse strains In vitamin A deficiency the breakdown of a barrier of healthy epithelium is quite justifiably held to be the cause of infections We can also cite natural protective factors which act like antibiotics In the work of Bloom *et al*[7] the anti anthrax polypeptide from resistant species protects the mouse against anthrax just as an antibiotic might This last example deals with interspecific resistance Schneider confines his remarks to intraspecific resistance but, unless he can show that the mechanisms in the two cases are exclusively different this example is also pertinent Schneider's very ingenious shorter method of assay[58] depends on a count of viable organisms in the spleen If the nutritional factor confers greater power on the macrophages of the spleen to kill organisms it would indeed have a very wide significance

In this modest attempt to point out some of the salient features involved in the study of nutritional effects on natural resistance there has been no attempt to cover the available literature We have not discussed the role of proteins and amino acids The available data are largely inconclusive or uncertain as to interpretation A new start on this topic by Dubos[43] holds out promise of general conclusions and many interesting details

At one time when a high association between ascorbic acid deficiency and infectious states had become recognized this deficiency was generally held to be a potent factor When it was then recognized that infection can be the cause of low ascorbic acid levels in the blood or tissues this latter finding dominated the attitude Raffel (p 182) suggests the possibility of a vicious cycle In Reed s review of ascorbic acid[9] the reader will find a discussion pro and con with an interesting account of the relation of ascorbic acid to phagocytic function

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Chapter 19 (*Continued*)

B Nutrition in Relation to Acquired Immunity

By A E Axelrod

Much attention has been directed toward the possibility of a relationship between nutritive state and resistance-susceptibility to infection With this in mind many experimentalists have sought for dietary factors that could influence the resistance or susceptibility of a host to infectious disease Many of these studies have certainly been motivated by the hope that suitable manipulation of the diet might influence the incidence and course of the infection for the benefit of the host Ultimately, these experimental investigations were designed to find application in the human armamentarium against infectious disease Unfortunately, these interrelationships have proved to be exceedingly complex and definitive statements on the relationship of specific dietary components to resistance to infection are difficult to make This controversial subject has been reviewed by Kolmer in a previous edition of this book

The preponderance of efforts in these endeavors has been directed toward a possible relationship between diet and "natural" or "innate" resistance This aspect is covered by Dr Zucker in this volume

The determinants of resistance to infectious disease are multiple in nature, and count among their members the classic antigen antibody interaction In many instances, this reaction may represent a most significant facet of the intricate mechanism involved in resistance to infection In this chapter, we shall discuss only the interdependence between nutrition and antibody formation or actively acquired immunity

Status Prior to 1955 —This subject has been discussed fully in two review papers appearing in 1955[1,2] and there is little need to recapitulate this material *in extenso* A brief summation of this field as it existed in 1955 is, however, in order From a morass of data accumulated by numerous investigators, there emerged the significant fact that individual nutrients could play an important role in the process of antibody formation Dietary deficiencies of these nutrients frequently led to impaired antibody production in experimental animals Generalizations at this point were particularly dangerous but it appeared that a severe protein deficiency as well as deficiencies of pyridoxine, pantothenic acid and pteroylglutamic acid produced the most consistent deleterious effects upon antibody formation This is not to imply that the function of other dietary factors was completely dissociated from the phenomenon of antibody synthesis On the contrary, the need for certain of these dietary components, particularly members of the vitamin B complex, could be demonstrated clearly on occasion A review of the literature made it apparent that a distressing variability existed in

the results of different investigators In some cases seemingly contradictory data were reported It is very probable that many of these discrepancies could be attributed to (1) the type, dosage, or route of administration of the antigen, (2) species of animal (3) methods of quantitating the antibody response, and (4) specificity and perhaps degree of the deficiency state This latter point was particularly evident in some of the earlier studies It seemed obvious that more conclusive data collected with vigorous control of these factors were required before the results of different experimenters could be fairly compared It was suggested that more positive information in this field would be forthcoming if the phenomenon of antibody formation were treated as an entity completely dissociated from that of resistance to infection With this operational procedure, studies would be designed *primarily* to investigate antibody production not merely to attempt correlations between antibody formation and resistance to infection, as has frequently been the case As will be emphasized later such correlations are of obvious importance in a study of the relationship of nutrition to infectious disease However an exclusive devotion to this aspect of the problem would in this reviewer's opinion at least, only impede experimental progress toward the elucidation of the mechanistic role of the nutritive factors in antibody synthesis

Thus, the data accumulated prior to 1955 definitely established the fact that antibody response as measured by the content of circulating antibodies, was markedly diminished in a variety of nutritional deficiency states Concurrently attention was being directed toward the mode of action of these nutritional factors The difficulties encountered in this course of action were many and were largely attributable to our great ignorance of the precise mechanisms involved in the process of antibody synthesis Information was sought on the role of biological factors involved in the mechanism of synthesis of a protein (antibody) when in actual fact knowledge of the pathways of protein biosynthesis were so tenuous This problem has been attacked with vigor over the past few years but much remains to be learned As a further complication antibody protein is one which must be fabricated through the stimulus of an agent foreign to the host Some information in this field has been garnered and can be summarized briefly

A state of inanition usually accompanies the deficiencies under consideration It became extremely important therefore to determine whether the effects observed in the deficiency were actually due to the specific absence of the nutritional factor or to the non specific effects of caloric restriction (inanition) The accumulated evidence argued strongly against any significant role of inanition *per se* and supported the viewpoint that the effects observed were due specifically to the nutritional factor in question This conclusion was further strengthened by numerous observations showing little correlation between growth and antibody responses of experimental animals in various deficiency states This latter observation has served as the basis for the suggestion that antibody response might be utilized as a more sensitive criterion of nutritional adequacy than the frequently employed growth response

In attempting to arrive at the mode of action of the nutritional factors,

we must give consideration to the possibility that the antibody synthesizing cells, whatever they may be, suffer a severe derangement in the deficiency state Such damage may be manifested either by structural changes demonstrable by histological techniques or by disturbances in functional activity Cells of the lymphoid series have been implicated as the sites of antibody synthesis Although histological studies of these cells in nutritional deficiencies have yielded discordant results, it would appear that lesions of these cells do occur in pyridoxine-deficient animals Thus, the deleterious effect of this deficiency upon antibody production may be referable in this case, at least, to damage to the lymphoid cells Experiments in our laboratory have indicated a disturbance in the functional activity of splenic cells from pantothenic acid-deficient rats immunized with diphtheria toxoid In studies conducted in association with Doctor Abram Stavitsky, it was shown that the splenic cells from immunized pantothenic acid-deficient rats, in contrast to those from normal immunized rats, were unable to fabricate antibody when cultured *in vitro* or when passively transferred to normal rats With Doctor Leuchtenberger, evidence was obtained that the mean DNA content of isolated splenic nuclei from immunized pantothenic acid deficient rats was lower than that from comparable controls These results may be interpreted to mean that the deficiency interfered with the acceleration of cellular division that normally accompanies antibody production in the spleen Since cellular division is always preceded by an increase in DNA content, the participation of pantothenic acid in DNA synthesis becomes an intriguing possibility

It must be clearly recognized that the serum antibody level which is utilized as a measure of antibody response probably reflects an equilibrium between the rate of antibody synthesis and release from the sites of synthesis on the one hand, and the rate of destruction of circulating antibody on the other A change in any one of these factors could obviously affect the content of circulating antibodies Thus, it becomes important to evaluate the effects of a nutritional deficiency upon antibody *release* and *degradation* before any positive statements can be made regarding any direct relationship between nutritional factors and antibody synthesis Such experiments have been conducted and have suggested that the decreased level of circulating antibody in the vitamin deficiencies cannot be attributed to a faulty release mechanism or to excessive destruction of antibody It seemed more likely, though not definitely proven, that there had been a disturbance in the process of antibody synthesis

Current Status —More recent studies conducted, in the main, since 1955 and not covered in the two reviews cited earlier[1] are in general agreement with previous observations demonstrating the inhibitory effects of nutritional deficiencies upon antibody production in experimental animals Rats,[3 4 5 6 7] mice,[8] and guinea pigs[9] have served as experimental subjects in these studies and a variety of antigenic stimuli *i e* vaccine from a strain of *C kutscheri*,[3] vaccines of *S typhi*, *B melitensis* and heterologous erythrocytes,[4 5 6 7] diphtheria toxoid,[9] and swine influenza virus[8] have been employed Zucker *et al* [3] have noted the inhibitory effects of pyridoxine and pantothenic acid deficiencies upon antibody production and the lack of such an effect in a partial thiamine deficiency Giunchi *et al* have also

observed the deleterious result of a pantothenic acid deficiency.[4,5,6] A requirement for ascorbic acid in the development and maintenance of acquired immunity has been reported by Bersins[9] while Underdahl and Young[8] could find no such need for vitamins A, D or E. Wissler *et al.*[7] utilized the phenylalanine antagonist B_2-thienyl alanine to demonstrate the requirement of phenylalanine for antibody synthesis. Bianchi *et al.*[10,11] were unable to observe an effect of a pyridoxine deficiency induced by the pyridoxine antagonist deoxypyridoxine upon antibody production to typhoid vaccine in rats and rabbits. This result is in marked contrast to the consistent findings of other workers in this field demonstrating the inhibitory action of a dietary-induced pyridoxine deficiency in experimental animals. More specifically, it is not in agreement with the observations of Stoerk[12] and ourselves[13] who have also employed the same antagonist to develop this deficiency state. The failure of Bianchi *et al.* to present definitive data on the degree of their induced deficiency state makes it difficult to evaluate their discordant result.

The studies discussed thus far have dealt with the relationship of various deficiency states to antibody production in experimental animals. A recent series of observations has, however, concerned itself with the effects of large dosages of various vitamins administered to animals maintained on *normal* diets during the periods of active immunization. This experimental design tends to express the pharmacological action of the vitamins rather than their more commonly recognized functions as nutritional factors. Solarino[14] in reviewing the work of his school has reported the stimulatory action of pantothenic acid, riboflavin, *p*-aminobenzoic acid, nicotinic acid and vitamin E upon antibody production in rabbits to vaccines of *Vibrio choleræ* and *S. typhi* and to heterologous erythrocytes. Vitamin P was without effect. This author stresses the possible harmful effects of higher dosages of certain of these vitamins upon antibody synthesis. In comparable experiments with rabbits, Segagni[1] noted that the administration of vitamin E led to an earlier and more extensive formation of antibodies following stimulation with typhoid vaccine, O streptolysin or staphylococcus toxoid. This stimulatory effect was, however, only temporary. Richou[16] on the other hand failed to observe any effects of pantothenic acid administration to rabbits immunized with staphylococcus toxoid and similar negative results with folic acid, pantothenic acid and pyridoxine were obtained by Lamanna and Tavanti[17] in rats vaccinated with *S. typhi*. Butturini and Casa[18] concluded that ascorbic acid and vitamin E actually block the formation of antistreptolysin in guinea pigs.

Recent studies in the human have failed to demonstrate any effects of malnutrition upon the isohemagglutinin content[19] or antibody formation to diphtheria toxoid.[20] A pyridoxine deficiency induced by deoxypyridoxine did not affect antibody response to typhoid vaccine or the A and B blood group substances.[1]

Studies on the relationship between nutritional state and antibody formation have been conducted in our laboratory over an extended period of time. More recently, the following lines of investigation have been pursued. Previous work with diphtheria toxoid had demonstrated a requirement for a number of vitamins, particularly of the B complex, in antibody syn-

thesis in the rat In a continuation of these studies, we have found that deficiencies of the amino acids tryptophane and methionine markedly inhibit antibody response Deficiencies in vitamin E (conducted in collaboration with Dr S Ames of The Distillation Products, Inc) and choline *were without effect* The absence of any deleterious action of a choline deficiency is of some interest since this deficiency state produced a marked weight loss as well as an extreme hemmorhagic condition of the kidney A similar lack of correlation between antibody response and severity of the symptomatology of deficient animals has been frequently noted Marked decreases in the avidity of serum antibody were observed in rats with pyridoxine and pantothenic acid deficiencies Thus in these deficiency states there was a qualitative difference in the type of antibody formed as well as a diminution in the total quantity of antibodies produced This qualitative change is manifested by a lowered ability of the antibody to combine with the antigen and most likely results from the synthesis of altered antibody molecules

Further studies were designed to investigate the role of nutritional factors in the various phases of the anamnestic response to diphtheria toxoid in the rat[13] Deficiencies of pantothenic acid, biotin, pyridoxine and tryptophane produced marked inhibition of the secondary (booster) as well as of the primary response to this antigen, the inhibition of the booster response being most pronounced Intensive nutritional therapy given during the secondary phase *only* failed to elicit antibody formation In no case was an anamnestic effect seen in these supplemented animals despite their immediate and marked growth response to the nutritional therapy *Repeated injections of diphtheria toxoid* were unable to overcome the inhibitory effect of a pyridoxine deficiency induced by dietary means or by the administration of the pyridoxine antagonist, deoxypyridoxine Thus, it seems clear that adequate nutrition during the primary phase is essential for the attainment of a satisfactory booster response Subsequent experiments demonstrated that a pyridoxine deficiency induced by the administration of deoxypyridoxine during the secondary phase could significantly inhibit the secondary response This inhibition was apparent three days after the booster injection It should be stressed that these animals received an adequate diet during the primary phase and were therefore permitted to initiate the events, template or adaptive enzyme formation, which under normal circumstances would be triggered by the secondary stimulus to accelerate the processes of antibody synthesis A pyridoxine deficiency in the secondary phase inhibited this normal sequence These results can most likely be ascribed to the deleterious effects of an acute pyridoxine deficiency upon the lymphoid apparatus Thus, the successful attainment of a satisfactory anamnestic response to diphtheria toxoid in the albino rat requires a state of adequate nutriture during *both* the primary and secondary phases of this process Control experiments demonstrated again that inanition was not a factor in these studies It was further noted that the high content of circulating antibody produced by anamnesis in normal animals was not affected by a subsequent acute deficiency of pyridoxine

Our studies described thus far utilized only particulate antigens In

order to obtain further information regarding the antigenic specificity of these deficiency effects, it was considered advisable to repeat these experiments with a non particulate antigen. Influenza virus was chosen since it represents a nonparticulate antigen of clinical interest whose corresponding serum antibody can be readily determined by a specific neutralization procedure. Antibody formation to this virus was markedly diminished in pantothenic acid and pyridoxine-deficient rats. Of considerable interest was the observation that antibody synthesis was not impaired in rats with severe thiamine deficiency. Inanition was without effect. These results parallel our previous observations with other antigens and further emphasize the general nature of this phenomenon as well as the specificity of action of the vitamins as regards antibody production.

In contrast to the requirement for a high level of circulating antibodies in combatting certain infections, it may be desirable in some disease states to inhibit the antibody response to various antigens. This is the case for hypersensitivity (allergic) reactions where the presence of certain antibodies is necessary for the manifestation of the disease. The inhibition of the undesirable antibody response by the induction of a vitamin deficiency state suggests itself. A specific vitamin deficiency can be produced either by limiting the dietary intake of the vitamin or by utilizing a specific vitamin antagonist. The latter procedure appears more feasible. In our own laboratory, we have been able to lessen the severity of the early (Arthus type) hypersensitivity reaction to diphtheria toxoid in the guinea pig by the administration of deoxypyridoxine. These studies were conducted in collaboration with Dr. David A. Long, The Wellcome Foundation Limited, London, England. Our studies on skin homotransplantation afford another illustration of the possible usefulness of an induced vitamin deficiency state in preventing or diminishing the extent of a hypersensitivity reaction. It is generally agreed that the failure of an homologous transplant is due to an acquired immune response, perhaps of the delayed hypersensitivity type, of the recipient to the antigens of the donor tissue. The subsequent antigen antibody interaction is assumed to effect the rejection of the donor tissue. On this basis, a successful transplant would be established if the immune response of the host could be blocked. The soundness of this hypothesis has been verified.[2, 3] A high proportion of successful skin homotransplants can be achieved in pyridoxine-deficient rats of certain strains. The deficiency state was induced by the omission of pyridoxine from the diet or by the administration of the pyridoxine antagonist, deoxypyridoxine.

Summary.—The detrimental effects of specific dietary deficiencies upon the development of acquired immunity in experimental animals have been amply documented. In particular, the requirements for amino acids and certain members of the vitamin B complex are recognized. These requirements are certainly influenced by various factors such as the type of antigen and host species. In some deficiency states the type as well as the total amount of antibody protein can be affected. The anamnestic (booster) response seems to be particularly sensitive to the absence of required nutrients. The essential role of ascorbic acid in antibody synthesis is being clarified. The effects of the fat soluble vitamins A, D and E are

inconsistent and these factors do not appear to have a major role in acquired immunity The nutritional requirements for carbohydrates, lipids and minerals have not been investigated

The present situation in regard to a relationship of nutritional state to acquired immunity in man remains indeterminate There exists a formidable amount of evidence which denies any such relationship In the main, these studies have dealt with the effects of general malnutrition and are reminiscent of the lack of effect of inanition upon antibody response in the experimental animal Further clarification must await studies utilizing well-defined specific deficiencies in human subjects The experiments of Wayne and associates[21] represent a beginning in this direction The pharmacological action of certain vitamins in stimulating antibody production in normal experimental animals requires confirmation in man

The significance of the animal experimentation must also be evaluated critically Generally speaking these experiments have employed a severe deficiency state of the particular nutritional factor in question and have undoubtedly yielded much useful information However, serious consideration must be given to the possible occurrence of non-specific secondary effects in these severely debilitated animals In agreement with the view expressed by Horwitt[74] this reviewer also visualizes the need for controlled studies in experimental animals only *partially* deprived of specific nutrients Such studies would bear a closer relationship to the degree of nutritional depletion commonly encountered in the human patient

It must be reemphasized that an antibody response may represent only one facet of a complex mechanism determining resistance to infection In many instances, no correlation exists between the ability to fabricate antibodies and the degree of resistance to an infectious agent Such a circumstance has been nicely illustrated by Zucker *et al*[3] It is obvious, then, that a decreased immune response resulting from a nutritional deficiency will be of significance in the phenomenon of resistance to infection *only* in instances where resistance can be explained in terms of recognized immunological reactions

In addition to their role as determinants of immunity against infection, antibodies are, of course, vital components of the hypersensitivity phenomenon Our experiments (see above) and those of Schneider *et al*[5] have demonstrated the influence of nutritional state upon hypersensitivity reactions In the latter study, susceptibility to acute disseminated encephalomyelitis in mice was investigated Such effects are in accord with the known role of nutritional factors in antibody production and lend encouragement to the hope that undesirable states of hypersensitivity may become amenable to inhibition by nutritional means The beneficial effects of a pyridoxine deficiency on skin homotransplants may be cited as a case in point

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Chapter 20

Nutrition in Relation to Dental Medicine

By James H. Shaw

Dental medicine is the specialty of medicine that is concerned with the welfare of the teeth and the soft tissues of the oral cavity and with the diagnosis of systemic diseases that have oral manifestations. During the past two or three decades, it has become increasingly evident that nutrition plays just as important a role in the development and maintenance of the oral tissues as in the development and maintenance of tissues elsewhere in the body. Indeed the tissue components of the mouth are little different from comparable tissues elsewhere in the body as far as the metabolic processes during development, growth and maintenance are concerned.

By reason of the specific location and function of the oral cavity, its tissues are subjected to a wider variety and probably a more stringent series of stresses than the tissues in other moist internal cavities of the body. Consider for example the wide variety in physical texture of the food that has to be chewed into a form suitable for swallowing, the wide range of temperatures of common food components as ingested, the wide variety of chemical stimuli to which the tissues of the oral cavity are exposed periodically, and the ideal circumstances for the growth and multiplication of the wide spectrum of micro-organisms that reside therein. The subdivision of food by the teeth and the buffering and diluting capacity of the saliva greatly reduce the intensity of some of these stresses before the food materials are passed on to the lower areas of the gastro intestinal tract. The soft tissues are unusually susceptible to current metabolic abnormalities of nutritional origin. During the early years in which characteristic signs of individual nutrient deficiencies were recognized, the soft tissues of the oral cavity were particularly valuable by reason of their susceptibility to these nutritional disturbances and by reason of their ready accessibility for examination. The classical signs of nutritional deficiencies in oral tissues will not be discussed in this chapter since they are presented in detail in the chapters of this book that are concerned with the B complex deficiencies and with scurvy.

In contrast, the hard tissues of the oral cavity, the enamel, dentin and cementum, are much less influenced by post-developmental systemic disorders than by the systemic disorders which operate during the developmental period. To a certain degree, the dental hard structures are kymographs in which are recorded both physical and chemical evidence of the metabolic circumstances which were prevalent at the time the specific areas of these structures were elaborated and calcified. However, in addition, the integrity of the teeth is influenced to a large extent by the oral environment which surrounds their external surfaces on a current basis. In any dis

cussion of the relationship of a specific diet to the integrity of the hard structures, both the dietary influences upon oral environment and upon the nutritional status as mediated through one or more systemic pathways must be considered and integrated

Over the past two or three decades, an appreciable change has occurred in the type of nutritional manifestation observed by clinicians At the beginning of this period frank nutritional deficiencies pellagra, beriberi rickets, etc, were commonly seen in dental practices in large urban areas and in rural communities alike During this period due to the widespread increase in the attention focused on the nutritional problems, particularly in the oral cavity, a striking decrease in oral manifestations of nutritional deficiency diseases has been observed in the average practice Hence our attention is being directed in an increasing degree to those nutritional abnormalities which occur during development or over prolonged periods of adult life, but which are not detected until long after the actual conditions of nutrient imbalance may have begun Such studies need to be made in a variety of the chronic diseases that plague the human race

The diseases of the oral cavity are particularly good examples of diseases which have delayed components The incidence of tooth decay in particular, has been shown to be related to specific nutritional abnormalities that occur during tooth development The diseases of the periodontal tissues may likewise have nutritional components which are presently unknown or ill defined but the prevalence of these diseases should spur investigators to pursue more diligently the possible ways in which these influences are mediated

Before a discussion of the oral diseases that result from nutritional abnormalities, let us consider some of the present knowledge about the structure of the teeth and surrounding tissues the uniqueness of these calcified tissues and some of the established facts concerned with the etiology of oral disease

THE STRUCTURE OF TEETH

The teeth are composed of three highly calcified tissues enamel dentin and cementum (Fig 38) Enclosed within these calcified tissues is a highly vascular connective tissue the dental pulp which is frequently called the "nerve" of the tooth because of its great sensitiveness to heat cold and other stimuli Around the periphery of the pulp in contact with the inner surface of the dentin, is a layer of cells, the odontoblasts These cells are responsible for the formation of the dentin and continue to lay down secondary dentin at a relatively slow rate throughout the life of the tooth When these cells are stimulated by the proximity of a carious lesion secondary dentin is formed more rapidly in an attempt to restrict the progression of that lesion The odontoblasts are endodermal in origin as are the cementoblasts which are responsible for the deposition of cementum around the outer surfaces of the roots of the tooth In contrast, the enamel is of epithelial origin being formed by ameloblasts that persist as a portion of the enamel organ until the time the teeth begin to erupt into the oral cavity

The teeth are retained in their bony sockets or alveolæ by means of the highly fibrous tissue structure termed the periodontal membrane The diseases which affect the integrity of this structure or the integrity of the bone surrounding the socket, result in one or another phase of periodontal disease and may progress sufficiently to cause loosening and loss of the teeth

Early anatomical studies of the enamel with the light microscope led investigators to postulate that the smallest structural units of enamel were inorganic prisms surrounded and cemented together by a sheath of interprismatic cementing substance Only 2 or 3 per cent of organic matter is contained in the enamel Almost the entire composition of the rest is inorganic substances The tiny amount of organic matter present was

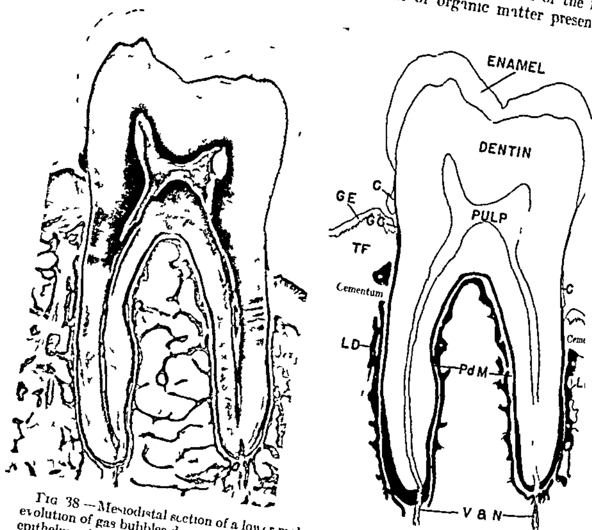


Fig 38 — Mesiodistal section of a lower molar tooth (The enamel is disrupted by the evolution of gas bubbles during decalcification of the specimen) Normally the gingival epithelium (GE) is in close apposition to the cervix of the tooth and acts as a barrier to decrease bacterial invasion of the underlying dermis Transverse fibers (TF) form another barrier against bacterial penetration In this case a small amount of salivary calculus (C) was deposited and caused the formation of an abnormally deep gingival crevice (GC) This is the beginning of periodontoclasia which at a later stage causes destruction of the lamina dura (LD) a compact bony plate lining the alveolus as well as the periodontal membrane (PdM) which attaches the entire tooth root to the surrounding bone V & N vessels and nerves supplying the dental pulp

originally believed to be contained in these interprismatic sheaths However, recent observations made possible by the higher resolving power of the electron microscope indicated that this concept was unduly restricted Instead, minute fibrils of organic matter have been observed to permeate each of the enamel prisms in extremely delicate and intimate fashion [1] In addition the interprismatic substance has been shown to have deposited within it an appreciable number of inorganic crystals

The dentin is traversed by tubules which radiate from the pulp to the dento-enamel junction Organic fibrils from the odontoblasts actually penetrate the entire width of the dentin It has been postulated that dental lymph may be transported from the pulp across the dentin by reason of

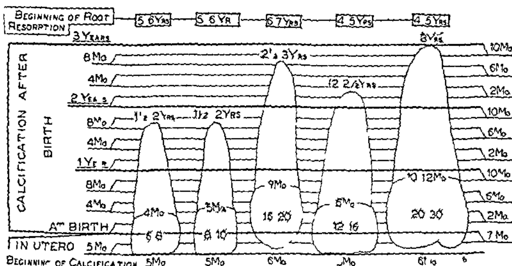


Fig 39 —Periods of calcification and eruption of the deciduous teeth The portions of the teeth that are formed completely are seen below the lines Figures in dotted areas the time of completion of the crowns and roots shaded figures the time (in months) that the tooth appears normally in the mouth Chart of the left upper jaw this information applies approximately to the other teeth with slight variations (Adapted from Logan and Kronfeld)

these fibrils The exact status of this hypothesis is indefinite at the present time The organic content of dentin is much higher than for enamel and approximates the concentration of the long bones

The time intervals involved in the development of teeth are important considerations in any discussion of the relationship of nutrition to tooth development and to the later caries-susceptibility of the teeth The life history of a tooth may be divided into three main eras the period during which the crown of the tooth is forming and calcifying in the jaw, the period of maturation when the tooth is erupting into the oral cavity and its root or roots are forming, and the maintenance period while it is in full function in the oral cavity The length of time during which a human tooth is developing and maturing prior to its functional responsibilities is often neglected As an example of the time interval involved let us consider the first permanent molar the six year molar, which is one of our more im-

portant teeth by reason of its large masticating surface and because of its keystone position in the dental arch. Its histological primordia are elaborated about the time the infant is born. From then until two and one half to three years of age, the organic frameworks of the enamel and dentin in the crown are being deposited and calcified. By the end of the third year, the crown has attained its adult size but is not yet fully calcified.

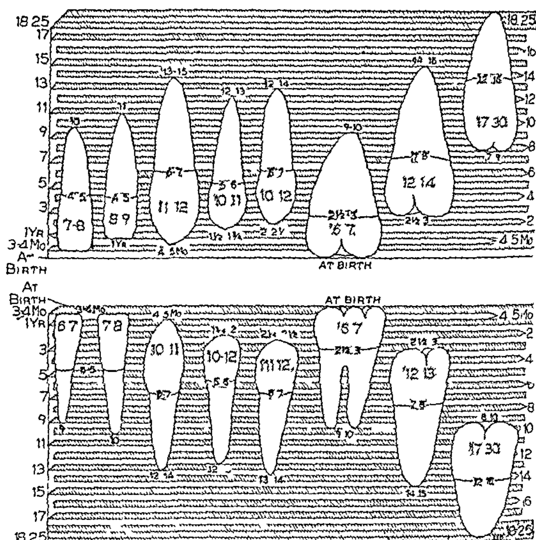


FIG 40 —*Periods of calcification and eruption of the permanent teeth. The upper and lower first molars (sixth from the left) calcify at or very soon after birth. The beginning of calcification of the other teeth and the average time of completion of their crowns and roots are indicated by figures in dotted areas. Shaded figures indicate when the crown appears normally in the mouth. This type of graph precludes drawing the teeth in correct anatomical form. (Adapted from Logan and Kronfeld.)*

Eruption into the oral cavity begins between six and seven years of age and its roots are completed around nine to ten years of age. Thus almost ten years elapse between the initiation of this tooth and the attainment of its final form. Comparable data for the deciduous teeth and the permanent teeth are presented in Figures 39 and 40.

THE UNIQUENESS OF THE DENTAL CALCIFIED STRUCTURES

In a discussion of nutritional influences upon teeth we must recognize that at least three striking differences exist between the calcified tissues of the teeth and other tissues of the body First enamel and dentin contain no microscopically detectable capillary or lymphatic vessels to act as transport systems for nutrients However the intimate relationships between the organic and the inorganic components of enamel suggest that pathways for relationships between the enamel and the rest of the body may readily exist even though there is no evidence of any vascular or neural element within enamel The dentin likewise contains no formed vascular elements However, its structure is such that it may lend itself more readily to a passage of extracellular fluids by reason of dentinal tubules that traverse the dentin from the odontoblastic layer of the pulp to the dento-enamel junction

Second, calcified dental tissues do not have a microscopically or chemically detectable ability to repair areas which are formed improperly or calcified inadequately during development nor does the tooth have an ability to repair itself after a portion has been destroyed by tooth decay or by a mechanical injury This is in direct contrast to the long bones where the Haversian systems are continually being remodelled and replaced and where diseased or fractured areas heal Yet despite the above contrast studies with radiotracer materials indicate that enamel and dentin are permeable to various inorganic ions The inorganic elements of each area of mature teeth are capable of participating in an exchange process with comparable elements carried to the area by body fluids The observation in mature teeth that the interchange between normal and radioisotopic elements in the enamel took place by reason of the contact of enamel with saliva is particularly interesting and thought provoking In contrast the interchange in the dentin occurred by reason of the ions brought to the dentin by the blood supply in the pulp Thus saliva acts as the pathway by which systemic nutritional influences are communicated to the enamel

Third, unlike other tissues the calcified tissues of teeth have a partial change of environment midway in their life history During the developmental period while the tooth is growing and calcifying it has complete systemic contact through normal vascular and neural pathways When the tooth begins to emerge into the oral cavity the blood vascular supply to the enamel organ is severed and the enamel surface comes in contact with that complex mixture of saliva microorganisms food debris epithelial remnants, etc , which is typical of the oral cavity Thus instead of a systemic environment only the tooth has in addition an oral or external environment The effects of this environment have to be studied and evaluated whenever a change in incidence of tooth decay results from a post developmental dietary manipulation

MODERN CONCEPTS OF DENTAL CARIES

During recent years a number of facts have been clearly established about the etiology of dental caries Some of these pertain to concepts which

have been postulated for generations from human studies but which have been demonstrated now beyond reasonable doubt by definitive experimental trials with laboratory animals

There can no longer be any question that micro-organisms are required *to cause the destruction of tooth substance* in the characteristic fashion termed tooth decay This point was established in studies with caries susceptible rats that were *maintained throughout life* under germ free circumstances[3] In this experimental environment, these animals did not develop tooth decay when fed a caries-producing *ration* *The germ free* technique provides the opportunity to evaluate which microorganisms or groups of microorganisms are responsible *for the destruction of enamel* and dentin in the characteristic manner defined as dental caries As yet relatively little has been done to define this relationship In one study Orland and co-workers[4] inoculated germ-free caries-susceptible rats with a mixed culture of Enterococci and found that characteristic carious lesions developed in the sulci of the molars

Clinical observations have indicated that the salivary glands are of considerable *importance in the maintenance of teeth* Where salivary glands are congenitally missing or are destroyed by radiation of the head and neck region there is a uniformly *increased susceptibility* to dental caries Similarly in experimental animals, the surgical removal of the major salivary glands results in spectacular increases in tooth decay[5] Of the several salivary glands, the parotid and submaxillary glands have been shown to be most important in the rat, with the sublingual gland contributing relatively little to the maintenance of the teeth[6] In human studies there is evidence to indicate that the quantity and physical consistency of the saliva is of considerable importance Trimble Etherington and Losch, as well as other investigators, observed a positive correlation between the *incidence of tooth decay and the volume of stimulated saliva*[7] *In* similar studies Cushman Etherington and Thompson demonstrated that children with ropy, mucinous saliva had a higher tendency to develop tooth decay than children with a watery saliva of lower viscosity[8]

The correctness of the old saying, "A clean tooth never decays" and the difficulty to obtain such a condition, has been demonstrated by experiments in a series of rats where their diet was introduced directly into the stomach by a tube-feeding procedure[9] The normal microbial oral flora was observed in these animals but no carious lesions developed When the same caries-producing diet was eaten *in the usual fashion* by littermates, a high incidence of tooth decay was observed Even when the supreme *penalty of desalivation was imposed* upon the tube fed animals, no carious lesions developed Of all the components of the diet the carbohydrate fraction appears to be the one that is necessary in the oral cavity for the production of tooth decay When a carbohydrate-free diet is fed for prolonged periods either to intact rats or to ones from which the principal salivary glands have been removed no carious lesions develop[10] If all of the diet except the carbohydrate is introduced into the stomach by tube and only the carbohydrate *ingested orally*, carious lesions developed at approximately the expected rate for rats that consume the entire diet by the normal route[11] Likewise when caries-susceptible rats consume a

liquid diet, they have appreciably less tooth decay than when their littermate control rats consume the same ration in solid form [1]

Extensive studies have been conducted in human populations in a mental institution in Sweden, where sucrose was fed in several forms at high levels to inmates for relatively prolonged periods of time [13] When high amounts of sucrose were fed in solution the increase in dental caries incidence was barely perceptible However, when sucrose was fed in the form of sticky candy such as caramels or toffees, there were tremendous increases in the incidence of tooth decay Comparable amounts of sugar in chocolates or in bread caused intermediate increases in dental caries incidence These studies uniformly point toward the rate of oral clearance of carbohydrates as a strong determining factor on the extent of tooth decay

Mono and disaccharides as the sole sources of carbohydrate in simple forms of purified diets usually cause a higher rate of dental caries incidence in experimental animals than the same quantities of starches or dextrins [14] However, where natural diets are used other carbohydrates have been shown to be equally or more cariogenic than sucrose In some of the experiments by Hunt s group at Michigan State finely ground rice has been shown to be more cariogenic than sucrose[15] and in other studies various forms of cooked cereals have been shown to be more cariogenic than sucrose [16] Various antibiotic materials such as penicillin, aureomycin dibasic ammonium compounds and urea have been shown to cause a reduced incidence in tooth decay among experimental animals and in some cases also in human subjects [17-19]

Strong genetic traits toward caries resistance or toward caries susceptibility have been reported in animal strains in laboratories [20,21] The mechanism by which these hereditary tendencies are mediated is unknown However, it is important to notice that both oral environmental and nutritional variations may modify the degree of manifestation of the genetic tendency For example if a strain of rats is highly susceptible to tooth decay, the incidence of dental caries may be greatly reduced by any one of a number of the above variations induced in the oral environment In addition various nutritional influences imposed during tooth development may reduce the incidence of tooth decay below that which would be expected in this caries susceptible strain if these nutritional influences had not been brought to bear during tooth development Likewise a caries resistant strain of rats will have an increased incidence of tooth decay if the salivary glands are removed or if a particularly cariogenic ration is fed

NUTRITIONAL INFLUENCES DURING TOOTH DEVELOPMENT

With this related background of information about the structure of teeth, the development of teeth and the etiology of dental caries let us examine some of the specific known relationships between nutrition and dental caries as they are encountered in the three eras in the life history of an individual tooth Unquestionably the most striking of these influences occur by reason of imposition of nutritional deficiencies during tooth development Three classical examples exist in which specific nutritional

There is no substantial body of information to indicate that enamel hypoplasia in human beings is attributable to vitamin A deficiency during tooth development. No satisfactory surveys have been conducted to determine whether or not vitamin A deficiency during tooth development is in any way related to the caries-susceptibility of these teeth post-developmentally.

Repeated demonstrations have been made of influences of vitamin A deficiency on epiphyseal bone formation. These changes were primary results of the general deficiency syndrome, since they occurred sufficiently early in the deficiency to precede the cessation of over-all growth. The studies of Wolbach and Bessey have demonstrated that these are specific

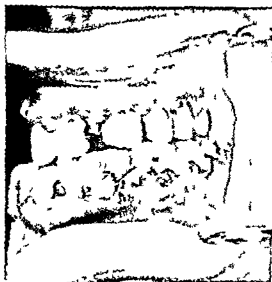


FIG 41 — Hemorrhagic gingivitis associated with avitaminosis C (scurvy). Note the swelling of the interdental papillæ and the large hematoma between the lower left central and lateral incisors. (Cahn, I. R. *Pathology of the Oral Cavity*, Baltimore, The Williams & Wilkins Co., 1941.)

effects of vitamin A deficiency and that the nerve damage in these deficiency states is secondary to and caused by the bone changes.[78] Vitamin A is essential for the activity of the epiphyseal cartilage cells without which they are incapable of undergoing the normal sequence of growth, maturation and degeneration which is essential in the mechanism of endochondral or replacement bone growth. Since vitamin A deficiency suppresses the cartilage cell sequences, endochondral bone growth is retarded and finally ceases entirely in long-continued vitamin A deficiency. Remodelling sequences involving concurrent resorption of bone with bone deposition and replacement of cancellous bone by compact bone cease to operate. There is a greatly reduced rate of resorption of trabecular bone with retardation and failure of Haversian system formation which results in an arrestment of compact bone formation. Eventually all skeletal growth dependent upon replacement of endochondral bone formation ceases. Appositional growth of bone of periosteal origin continues until inanition

intervenes at a rate in conformity to the normal growth pattern at each particular site Presumably the fact that growth of bone of periosteal origin continues is evidence that there is no fundamental error of calcification in the vitamin A-deficient rodent

These effects upon bone growth in vitamin A deficiency are of potential interest in the field of children's dentistry and orthodontics There has never been any thorough investigation to determine why orthodontic problems arise except the generalized statement that they are related to disproportionate development of the teeth and of the bones in the face and jaws Since vitamin A deficiency causes such a profound influence on bone development, some of the inadequate growth patterns which result in orthodontic problems may have had their origin in prolonged periods of subclinical vitamin A deficiency during the developmental period of the child

Vitamin C —Scurvy, the clinical entity which is attributable to vitamin C deficiency, has been described in detail in the chapter concerned with ascorbic acid In frank vitamin C deficiency, the lesions of the gingiva are particularly striking [7] (Fig 41)

It is noteworthy that these occur only when teeth are present and that the condition is remarkably consistent The gingival lesions begin on the interdental papilla, first as hyperemia with dilated thin walled vessels which have a tendency to hemorrhage Disintegration of the epithelium follows, and infection with ulceration, granulations and gangrene may result The gums become inflamed and spongy and bleed easily In cases of severe deficiency, these lesions become sufficiently extensive as to obstruct mastication and are frequently accompanied by loosening of the teeth and tooth loss

The deficiency of vitamin C primarily affects the ability of cells of connective tissue origin to elaborate their typical collagenous intercellular substances The odontoblasts which form the dentin in developing teeth are of endodermal origin and are readily affected by the deficiency of vitamin C Wolbach and Howe have studied the pathogenesis of these changes extensively [28] When guinea pigs are placed on a scorbutic diet, alterations soon appear in the odontoblasts which become atrophic and resemble the nearby pulp cells There is a decrease in their orderly polar arrangement, a decrease in height, and eventually a complete disorganization The decreased height of the odontoblasts in moderate deficiencies is believed to be sufficiently closely related to the vitamin C intake to permit this measurement to be used as a bioassay criterion [9] At the same time, the rate of dentin formation is sufficiently closely related to the amount of vitamin C consumed that it also can be used for a criterion for the bioassay of the vitamin C content of the diet [30] The dentin which is formed is laid down irregularly with the dentinal tubules lacking their normal parallel arrangement In severe deficiencies, dentin deposition stops entirely and the predentin becomes hypercalcified At late stages in the deficiency the ameloblasts atrophy and hemorrhages occur These changes have been interpreted to be due to traumatic injury of the enamel organ as the result of inadequate support of the underlying dentin Though these changes occur readily in the developing teeth of experimental animals, evidence has

not been presented yet to indicate a similar occurrence in human teeth as a result of scurvy during tooth development

As would be expected there is a rarefaction of the alveolar bone comparable to what is seen in the ribs and bones of experimental animals and humans The pathologic sequence in the destruction of the alveolar bone has been reported to closely resemble the changes observed in diffuse alveolar atrophy [31] Weakness of the supporting bones as well as the weak

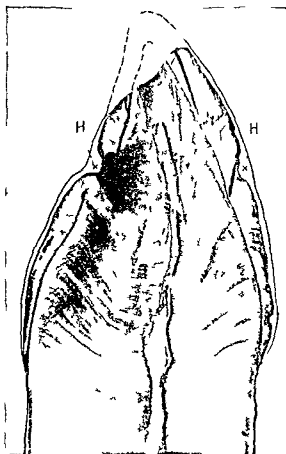


FIG 42 —Section of an upper canine tooth A severe systemic disturbance which occurred when the patient was about three years old caused the hypoplasia of the enamel (H) *As shown by poor calcification and rills in the subsequently formed enamel* (near the cervix of the tooth) the condition improved but did not become normal The solid line extent of normal enamel dotted lines loss of tooth structure due to attrition

ness of the collagen fibers in the supporting structures allows for a greater mobility of the teeth and a decreased ability to withstand the mechanical stresses encountered in chewing

The pathology in the pulp and in the odontoblastic layer in human beings is nearly identical with the pathologic changes in the scorbutic guinea pig according to Westin [3] In the teeth of scorbutic adults the dentin is resorbed and porotic The small amount of replacement dentin formed is of the osteodentin type The pulp is atrophic and hyperemic

Degeneration of the odontoblasts, the formation of cysts, and foci of diverticuli like regions of calcification were described

Although the relationship of vitamin C deficiency to gingival changes and to bone pathology has been repeatedly demonstrated, there has never been a clear-cut demonstration of a relationship between scurvy and dental caries A large experiment was conducted at an orphanage by Hanke where the usual orphanage diet was daily supplemented with a pint of orange juice and the juice of 1 lemon over a period of one year [33] The experimental group of children evidently had a reduced incidence of new carious lesions in contrast to the control group of children which had h... no citrus fruit supplementation However, surveys by Westin,[34] Hess ar...

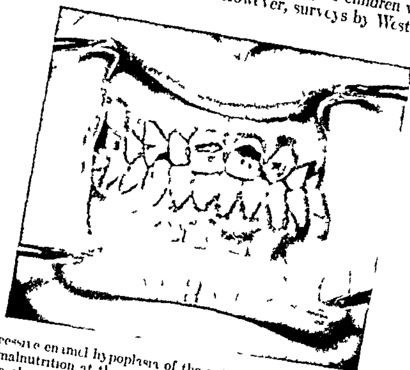


Fig 13 Excessive enamel hypoplasia of the anterior teeth of a sixteen year old girl due to severe malnutrition at the age of six months The marked gingivitis on lower anterior gingiva cleared up quickly as a result of vitamin C therapy (Cahn L R *Pathology of the Oral Cavity* Baltimore The Williams & Wilkins Co, 1941)

Abramson [35] and experiments by McBeath[36] and Grandison, Stott and Cruickshank[37] failed to demonstrate any difference in dental caries incidence between groups which received a normal diet and one supplemented with considerable amounts of vitamin C

Vitamin D, Calcium and Phosphorus —The first experimental production of rickets to demonstrate an influence upon tooth development was reported by Lady May Mellanby in 1918 [38] She observed that a deficiency of a fat-soluble vitamin, later designated as vitamin D, in young puppies had a profound effect on the developing enamel and dentin of the permanent teeth on the rate of eruption, and also on the position of the teeth in the jaw When vitamin D deficiency was imposed upon a female dog during pregnancy, the deciduous teeth of the puppies had defects in structure and their eruption was delayed [39] However the puppies from comparable

dogs, supplemented with adequate amounts of the fat soluble vitamin, had normal deciduous teeth

The changes that occur in teeth during the rachitic process are appreciably less complex than those in bones described in Chapter 11, page 313 The first and most prominent change observed in rickets in rats is a calciotraumatic line, a line of disturbed calcification in the dentin[40] This is accompanied by retardation in the formation of predentin and a pronounced disturbance in the calcification of the dentin The latter is no longer homogeneously basophilic but is stippled by an irregular deposition of inorganic salts Calcification of the cementum is likewise retarded

Enamel hypoplasia does not occur except in the more severe cases of rickets in the dog whereas inadequate calcification of both the enamel and dentin can be demonstrated at relatively mild levels of the rachitic process Enamel hypoplasia has not been described in the rat as a result of rickets, *but it is likely that a sufficiently severe deficiency over a prolonged period* would cause this abnormality even in this species In human beings there is likely to be more than one cause of enamel hypoplasia (Figs 42 and 43) In a thorough survey of the case histories of individuals with enamel hypoplasia, Sarnat and Schour reported that only a small number of the cases had any evidence of a rachitic process during tooth development[41]

The bony structures supporting the teeth develop changes that are characteristic of those in bone elsewhere in the body Wide osteoid borders are found on the trabeculæ of the alveolar bone and the number and size of the trabeculæ are greatly decreased

Mellanby has conducted a wide variety of studies to determine to what extent there may be a correlation between the structure of human teeth as studied microscopically and the susceptibility to tooth decay[42] In order to set up standards whereby such a comparison could be made various stages of increasing severity of microscopic defects were described and correlated with the degrees of caries incidence in the same teeth It should be clearly pointed out that the defects which Mellanby described and which have come to be referred to as Mellanby hypoplasia are only visible at a microscopic level and can only be clinically discerned by a careful exploration of the tooth surfaces with a sharp explorer Thus this class of defects can be readily differentiated from those major areas of hypoplasia which are grossly visible upon clinical examination She reported that 78 per cent of deciduous teeth with well calcified enamel and dentin were free from caries, while only 6 per cent of the teeth with appreciable degrees of microscopic abnormalities were free of tooth decay *Although these data have inherent* assumptions, the over all trend of the material suggests that there is a significant correlation between the structure of teeth as detected microscopically and the susceptibility to decay However this should not be interpreted to mean that grossly hypoplastic teeth will decay for that reason nor is the corollary true that teeth that appear to be microscopically perperfectly calcified will never decay It is noteworthy to recall from histologic studies that perfectly formed teeth are found very rarely in modern civilized populations In contrast the teeth of experimental animals rarely have developmental abnormalities unless a specific systemic disorder has

been imposed during tooth development to alter the formation of organic matrix or the ability of the organic matrix to calcify properly The rhesus monkey is a particularly good example of this for its teeth uniformly have a high degree of perfection in their formation that is seldom equalled and never excelled in human teeth The studies on the correlation between Mellanby hypoplasia and caries incidence have been extended to clinical surveys in the schools of London, England where oral examinations were made in 1929, 1943, 1945, 1947, 1949, 1951 and 1955 [43] A consistently high correlation between good tooth structure and freedom from caries was observed

The effect of vitamin D supplementation upon the initiation and progress of carious lesions has been studied a great deal more intensively than the effect of any other essential nutrient Studies were conducted by Mellanby and co-workers in England in a series of experiments which lasted from 1923 through 1936 The most extensive of these experiments was conducted in three Birmingham children's institutions where the effect of supplements of cod liver oil and of irradiated ergosterol on dental caries incidence was evaluated [44] The data obtained definitely pointed toward a lower incidence of new carious lesions and a lower rate of progress of existing lesions among the children in the group which received irradiated ergosterol and those in the group which received the cod liver oil supplement, than in the children who received no vitamin D supplement The reduction in dental caries incidence among the fully erupted teeth in the vitamin D supplemented groups was statistically significant

This experiment was not conducted for sufficiently long to give definitive results about the effect of the vitamin D supplements on the caries-susceptibility of the developing teeth In the small group of teeth that partially developed during the experiment, there was a trend toward a lower caries experience for the groups of children given the vitamin D supplements Data collected in clinical surveys have added supporting evidence that inadequate vitamin D during tooth development results in a higher caries incidence

For a variety of reasons these studies have been criticized If they stood as the only evidence that an adequate amount of vitamin D during childhood was beneficial with respect to caries incidence, or if these investigators had claimed that vitamin D was the only nutrient involved, there would be reason to question the validity of the conclusions However, a variety of studies have been conducted in the United States and Canada which corroborate the original observations made by Mellanby and co-workers [45–47] In only a few experiments where the effect of vitamin D supplementation was studied were negative results found It is interesting to note that some of these negative studies were conducted in older groups of children than the remainder of the studies,[48] and that another one was conducted at such a high level of vitamin D supplementation as to raise a question as to whether the amount ingested was in the physiological range of normalcy [49] It is also noteworthy that none of the investigators who believed that vitamin D supplementation helped to reduce caries susceptibility claimed that this was the only reason for altered dental caries incidence, but rather that it was a partial means to cope with the problem

Evidence from other types of studies also suggests that vitamin D is important for the maintenance of normal teeth in the child population In a number of surveys efforts have been made to determine if there is any correlation between the dental caries incidence, the number of hours of sunshine in a given community, the latitude of the locality and its winter temperature For example, in a statistical evaluation by Mills, which was based on a large compilation of dental caries data collected by the United States Public Health Service, he reported that there was a definite increase of dental caries among twelve- to fourteen-year-old boys as the latitude increased[50] This increase amounted to approximately 15 more carious lesions per 100 children for each degree of latitude Increases were reported from 289 decayed, missing or filled (DMF) teeth per 100 children in the cities between 25° and 36° latitude in the southern states to approximately 491 DMF teeth per 100 children in the cities between 43° and 46° latitude just south of the Canadian border

On the basis of the same dental caries data, Fast has shown that there is a definite correlation between the mean annual hours of sunshine and the average incidence of tooth decay[51] He observed the following relationship the average number of cavities per 100 boys was 290 in areas with 3000 and more hours of sunshine per year and increased to a total of 486 in areas with less than 2,200 hours of sunshine annually Other studies suggest that there is a correlation between the dental caries incidence and the mean winter temperature with a greater incidence of tooth decay when the winter temperature is lower The most likely explanation of these effects would be an increased exposure of the children to sunlight with a greater amount of vitamin D being made available by reason of this exposure Other more subtle factors than the simple irradiation of the skin may contribute to this end result Although ethnic origin has been considered to some extent in these surveys possible variations that might influence caries-susceptibility on a regional basis have not been ruled out completely *In addition variations in food patterns may influence the* outcome and interpretation of the results For example throughout the southeastern states where the caries incidence is in general lower than in the north there is a high usage of self rising flour which contains appreciable supplements of inorganic phosphates In the light of the recent studies in experimental dental caries where the incidence of carious lesions was significantly reduced as a result of supplementation of the cariogenic diet with inorganic phosphates the increased phosphate consumption through the use of self rising flour may affect caries incidence materially[52, 53]

Studies in rodents have shown that the calcium phosphorus ratio of the diet during tooth development is an important factor in determining the composition of the inorganic fraction of the enamel and dentin Sobel observed that a diet with a high calcium phosphorus ratio resulted in the formation of teeth in the white rat and the cotton rat whose inorganic components had a higher carbonate phosphate ratio[54, 55] In contrast the animals which were fed a diet with a low calcium-phosphorus ratio during tooth development developed teeth the inorganic portion of which contained a much lower carbonate-phosphate ratio In an experiment of this type conducted with cotton rats Sobel and co-workers reported that the animals whose

teeth had the high carbonate-phosphate ratio were more susceptible to tooth decay than the teeth of the animals with the lower carbonate phosphate ratio.[56] It is unknown what relation these studies may have to human beings. The calcium-phosphorus ratios of the diets used by Sobel were appreciably more drastic than would ordinarily be encountered in human dietaries. The important contribution of these studies is the observation that the composition of the inorganic *components of enamel and dentin vary in dependence upon the blood levels of the required elements which in turn are dependent upon the amounts supplied by the diet.* It may well be that human teeth are more sensitive during development and calcification to abnormalities in the calcium-phosphorus ratio of the diet than the rat, or it may be that other circumstances in the developing, calcifying tooth determine the extent to which calcium and phosphorus variations in the blood stream are reflected in an alteration in the composition of the inorganic components of the enamel and dentin.

Fluorides.—A further influence during the development of teeth upon which a great deal of emphasis is being placed currently is mediated through the ingestion of fluorides. No current chapter on the relation of nutrition to oral health would be complete without a discussion of the role of the *fluorides in the etiology of dental caries.* The fluorides are ubiquitous materials which occur in small amounts in all foodstuffs. Extensive surveys of the fluoride content of more than 130 foods are available. The majority of foods such as vegetables, meats, cereals and fruits contain between 0.2 and 1.5 ppm of fluorides. Outstanding exceptions to this lower range are the seafoods, the edible portions of which contain 5 to 15 ppm of fluoride, and tea leaves which contain 75 to 100 ppm of fluoride. A cup of tea will supply approximately 0.1 mg. of fluoride. Reliable analyses of the fluoride contribution by foods in common human dietaries from as distant areas as Toronto, Minneapolis and Washington, D. C., indicate that an average diet supplies between 0.2 and 0.6 mg. of fluoride daily, without the use of unusual amounts of either seafoods or tea.[57–59] Because of the widespread distribution of fluorides, it has not yet been possible to produce a diet that is completely deficient in this element. At the lowest levels of dietary fluoride yet available no pathologic consequences, other than a high susceptibility to *the development of carious lesions have been noted by reason of the low level of ingestion of this element by rats.*[60]

In the data obtained from epidemiologic surveys in human populations and from rodent studies, there is a close correlation between the amount of fluoride ingested during tooth development and the amount of tooth decay that occurs in the teeth after development is completed. The first convincing evidence of such a relationship was provided by Bunting and co-workers in 1929, who reported the results of a survey in Minonk, Illinois.[61] The amount of tooth decay among the children born and raised in this community was a great deal less than in children who moved into Minonk after tooth development was complete. At the time of the survey, the investigators recognized that this striking difference must be related to the water supply, but the active agent was undefined. Later it was found that the drinking water contained 2.5 ppm of fluorides.

In 1939, more extensive information was provided by Dean and his col-

laboratories as the result of a survey of 1,581 children in 4 communities in the Illinois area where the water contained varying amounts of fluorides.[6] Later a more comprehensive survey was reported for 4,425 children from 13 cities and 4 states by the same group of investigators.[63] The data from the latter study are presented in Table 54 in terms of the number of DMF permanent teeth observed in the twelve- to fourteen-year-old children of these communities. Where the water contained 1 ppm of fluorides or more during tooth development, the children had a lower incidence of tooth decay than children in nearby communities where the water contained appreciably

TABLE 54.—A COMPARISON OF THE FLUORIDE CONTENT OF THE DRINKING WATER AND THE AMOUNT OF TOOTH DECAY AMONG 4,425 CHILDREN TWELVE TO FOURTEEN YEARS OF AGE IN 13 CITIES FROM 4 STATES. BASED ON REFERENCE 63

	Fluoride content (ppm)	*No. of children examined*	*Children with no tooth decay (per cent)*	*Average no. of diseased teeth per child*
Colorado Springs, Colo.	2.6	404	28.5	2.5
Galesburg, Ill.	1.9	273	27.8	2.4
East Moline, Ill.	1.2	152	20.4	3.0
Kewanee, Ill.	0.9	123	17.9	3.4
Pueblo, Colo.	0.6	614	10.6	4.1
Marion, Ohio	0.4	263	5.7	5.6
Lima, Ohio	0.3	454	2.2	6.5
Middletown, Ohio	0.2	370	1.9	7.0
Zanesville, Ohio	0.2	459	2.6	7.3
Quincy, Ill.	0.1	330	2.4	7.1
Portsmouth, Ohio	0.1	469	1.3	7.7
Elkhart, Ind.	0.1	278	1.4	8.2
Michigan City, Ind.	0.1	236	0.0	10.4

less than 1 ppm of fluoride. These findings have been corroborated by investigators in numerous areas of the United States, as well as in Canada, England, South Africa, Italy, Greece and Hungary. Although the above studies were concerned with the permanent teeth of the children, the deciduous teeth likewise have been shown to benefit from the ingestion of fluoride-bearing waters during tooth development.[64] In addition, it has been shown that the beneficial effect from the consumption of fluoride-bearing waters during tooth development remains into adult life.[65] Surveys in the United States, Argentina, England and Hungary have demonstrated that the exposure to naturally borne fluorides during tooth development continues to manifest itself by a low incidence of tooth decay in adult life. On the basis of these and a great many other studies there is no longer any doubt that water containing one ppm or more of fluorides has a definitely beneficial effect when consumed during tooth development upon the later caries susceptibility of the teeth.

The fluoride content of the teeth developed in areas where different amounts of fluorides were present in the water supply closely parallels the amount of fluorides in the water.[66] Where drinking water contained 0.0 to 0.3 ppm of fluoride, as in Washington, D. C., the teeth of the native

continuous residents had approximately 0.010 per cent of fluorides in the enamel and 0.024 per cent in the dentin. Where the water supply contained 1.0 to 1.2 ppm of naturally occurring fluorides, as in Aurora, Illinois, the teeth of comparable residents contained 0.014 per cent fluorides in the enamel and 0.036 per cent in the dentin. Presumably the caries resistance of the teeth is somehow related to their fluoride content.

Further light is thrown upon this subject in studies by Jenkins and Speirs, who determined the level of fluoride content in various levels of the enamel.[67] They noted that the outer surface uniformly had a much higher fluoride level than the deeper layer. In addition, they observed that this difference in distribution was detectable in unerupted teeth as well as in erupted teeth. The latter observation indicates that this was a developmental arrangement of the concentration of fluoride, and not a distribution that took place after the teeth had erupted into the oral cavity by reason of contact with saliva. These observations have been corroborated by Brudevold and co-workers[68, 69] who also demonstrated a post eruptive acquisition of fluoride by the surface layers of enamel which increased in proportion to the amount of fluoride in the drinking water.

In view of the beneficial influence of inorganic fluorides as introduced into water supplies by nature, the next step was to determine whether the introduction of comparable inorganic fluorides into low-fluoride waters would be equally efficacious. The first survey was begun at Grand Rapids, Michigan, in January, 1945, where the fluoride content of the water supply was increased to 1.2 ppm under the joint sponsorship of the United States Public Health Service, the University of Michigan and the Michigan State Department of Health. Muskegon, Michigan, served as the control low fluoride city. Soon after this, surveys were begun in a number of other cities. Some of the impressive data which are now available from the older surveys are presented in Table 55.[70] The over-all analysis of the data from these surveys indicates that the dental caries incidence in teeth formed during the survey period was on the average about 50 per cent lower than the caries incidence in otherwise comparable teeth formed prior to the increase in fluoride content of the water supply, or in those teeth formed in children in neighboring cities where the water supply did not have its fluoride content adjusted. As would be expected, the greatest benefits were in the youngest age groups. The high similarity of the data to those in communities where the fluoride is naturally borne is most striking. It is also noteworthy that no comparable decreases in dental caries incidence were noted in the children of nearby communities where the fluoride content of the communal waters had not been increased. The latter was true despite the use even on a limited scale of various tooth pastes and other prophylactic measures which have been widely suggested as being highly beneficial for the reduction of dental caries incidence.

On the basis of present knowledge, it appears that the most sensitive tissue in the body to excessive ingestion of fluorides is the ameloblastic layer which forms the organic framework of the enamel. When the drinking water of a community contains 2.5 ppm or more of fluorides, a manifestation known as mottled enamel results.[71] This only occurs when the high fluoride ingestion is during the developmental period of the teeth and

cannot occur after tooth development has been completed The degree of mottled enamel may vary from very slight non esthetically significant amounts to an extensive chalkiness of the surface with large opaque areas which may erode away rapidly and which in severe cases become heavily stained As the fluoride content of the water increases the severity and the extent of mottled enamel increases until at levels of 8 or 10 ppm in the communal water supply almost all of the individuals who grow up in the area have mottled enamel of such severity that it is aesthetically disfiguring

TABLE 55 —REDUCTION IN TOOTH DECAY OBSERVED IN VARIOUS FLUORIDATION STUDY PROJECTS BASED ON REFERENCE 70

	Fluoridation			
Community	*Date started*	*Report period (yr)*	*Age group (year)*	*Reduction in decay (per cent)*
Grand Rapids Mich	Jan 1945	8	6	70 8
			7	52 5
			8	49 2
			9	48 1
			13	39 7
Brantford Ont	June 1945	7	6	59 4
			7	69 5
			8	51 5
			9	46 2
			13	32 9
Newburgh, N Y	May 1945	7	6	69 4
			7	67 8
			8	40 4
			9	51 4
Evanston Ill	Feb 1947	4	6	73 6
			7	56 4
			8	35 4
Sheboygan Wis	Feb 1946	6	9–10 (4th grade)	35 3
			12–14 (8th grade)	29 7

* Decayed missing and filled teeth

At fluoride levels from 2 5 ppm or more, the water supply is in need of treatment, either by the development of a new source, by adequate dilution with low fluoride waters or by removal of the fluorides from the drinking water However, on the basis of these epidemiologic surveys fluorides contributing in the neighborhood of 1 2 ppm of fluoride to a water supply have definitely been shown to be of no detrimental public health significance with respect to the causation of mottled enamel in northern regions In hotter climates where the water consumption is appreciably higher, the optimal level of fluoride ingestion is in the neighborhood of 0 6 to 0 7 ppm

Other abnormalities than those caused in the developing teeth by excessively high fluoride ingestion have been sought in various surveys in the United States Probably the most important and extensive surveys in which general systemic influences of fluoride ingestion were sought were made in 1943 and 1953 in Bartlett and Cameron Texas[77] The former

community had a water supply that contained approximately 8 ppm of fluoride, whereas the latter community, situated some 30 miles distant, had a water supply with essentially no fluorides. In 1943 a series of inhabitants who had resided at least fifteen years in each community was selected at random and carefully examined by skilled physicians. A total of 116 were examined in Bartlett and 121 in Cameron. These individuals ranged from fifteen to sixty-eight years of age in 1943. 57.8 per cent of the Bartlett participants and 47.2 per cent of those from Cameron were over fifty five years of age. *X*-rays of various portions of the skeletal system and full case histories were taken. The data in these surveys indicated that there was no significant difference in any phase of health between individuals of one community and the other, with two exceptions. Many of the individuals who had resided in Bartlett during childhood had severely mottled teeth. In addition, a slightly higher incidence of cardiovascular disease was observed in Cameron. In all other regards, there were no detectable abnormalities that could be attributed to the different fluoride content of these two water supplies. Though this survey is undoubtedly the most intensive of all that have been conducted, many other surveys on different phases of the fluoride problem as related to systemic disease have been conducted. In all cases, levels of 1.0 ppm or more, up to as high as 8.0 ppm, in the United States have been shown to be negative with respect to any correlation of a systemic abnormality to the fluoride content of the water.

It is noteworthy that over 3 million individuals in the United States have consumed natural fluoride-bearing waters in excess of 1.0 ppm for decades, and an additional 5 million individuals have consumed amounts between 0.5 and 1.0 ppm.[73] Already the fluoridation of community water supplies has been widely instituted throughout the United States and elsewhere in the world. As of December 1, 1958, fluorides were being added to the water supplies in 1741 cities and towns in the United States with a total population of 34,453,565.[74] Many other communities are in some phase of equipment purchase and installation. The water supplies in Chicago, the second largest city in the United States, have been fluoridated since August 1, 1956.[75] This water system covers about 3,600,000 residents of the city and an additional 500,000 in the adjacent suburbs.

Uncharacterized Relations.—Another example of a developmental influence upon the teeth may be obtained from the extensive dental caries statistics that were collected on the children of European countries during World Wars I and II. Studies representing a total of about 750,000 children from eleven countries have been summarized and evaluated in detail by Sognnaes.[76] It is noteworthy that the reduction in dental caries experience in all these studies did not occur concurrently with the reduction in refined foods and sugar. Possibly the most detailed data are available from the children in Norway where almost the complete reduction in carbohydrate intake from sugar and highly refined flours occurred in 1939. Yet the greatest increase in caries free permanent teeth among seven year-old children did not occur until 1945. Indeed, the reductions in 1940, 1941 and 1942 were relatively small. The attention of the reader should be drawn to the fact that all the teeth in this particular tabulation had been in the oral cavity for only one or one and one-half

years Thus, there was a comparable length of exposure of the teeth in each particular group represented in the comparison The teeth that erupted six to eight years after hostilities enforced drastic changes in food habits were much more resistant to dental caries than the teeth that erupted during pre-war years and in the earlier war years

In World War I the maximum reduction in caries incidence was not observed until 1922 and 1923 that is, after the cessation of hostilities and the partial return of fine foods and sugar to the European dietary In the World War II period, the highest reduction in dental caries incidence was not reported until 1945 Thus in both periods there was a six- to eight-year lag in the attainment of the maximum caries resistance In other words, the teeth that were benefited most were those that were just beginning to form when the war time dietary change was imposed This time lag obviously cannot be explained purely on the basis of alterations in the oral environment of teeth that have been in the oral cavity for short periods of time Instead these data point to strong effects of the diet during the war years on the development of teeth that are much more caries resistant than those teeth developed by children consuming the typical pre war dietary foods The fact that these reductions in dental caries incidence were so comparable for the two wars and in the several countries from which data are available suggests that the data have a very high degree of validity The active factor or factors in this effect on dental caries incidence are unknown Along with the greatly reduced incidence of dental caries, Toverud[77] has reported that the permanent teeth erupted much later and that the deciduous teeth were retained in the mouth longer during the war years than in the pre-war period

Suggestions from other clinical surveys lend support to such developmental influences In a survey conducted by Cohen[78] on a group of preschool children in New England where the proneness to develop carious lesions is very high it was noted that the four and five year-old children from families in the high socio economic group had a significantly lower incidence of dental caries than the children from the less favored groups (Table 56) This difference between groups reflects good prenatal and pediatric care including diet counselling for the more favored groups It is noteworthy that the dental caries experience among the pre school children in the high socio economic group compared favorably with the caries index in children of the same age in endemic fluoride areas and in areas where the communal water supplies have been fluoridated

Similar results were observed in a clinic designed to give early pediatric care to children in two Norwegian communities Toverud[79] reported that those children who received good care in the early years of their life had a significantly lower incidence of tooth decay than similar children in the community who did not receive the services of this clinic or who did not seek help until later in their development

This type of clinical information has been greatly strengthened by investigations with rodents and monkeys[80,81] The ingestion of diets composed of natural foodstuffs during tooth development resulted in teeth that were much more resistant than the teeth of comparable experimental animals that developed during maintenance on diets composed of highly

purified ingredients Although the natural diet contained significantly more fluorides than the purified diet, other studies with rats have indicated that the difference in fluoride content of the two diets was insufficient to cause the different incidence of tooth decay [8] Further experiments to determine the active agent in this study have shown that the influence is a result of the different mineral components of the two diets When the mineral components of the natural diet were fed as the sole source of minerals in the purified diet, an appreciably lower incidence of tooth decay resulted [83]

TABLE 56 —AVERAGE NUMBER OF DECAYED EXTRACTED AND FILLED TEETH IN PRE SCHOOL CHILDREN OF DIFFERENT SOCIO-ECONOMIC GROUPS [78]

Socio economic level	*Age*	*No of children*	*Per cent with one or more def teeth*	*Average no of def teeth per child*
Low	4	135	84	3.90
	5	36	89	5.44
Medium	4	135	61	2.39
	5	36	69	3.06
High	4	77	53	2.03
	5	18	75	3.19
Total	4	347	68	2.89
	5	88	78	4.06

NUTRITIONAL INFLUENCES DURING TOOTH MATURATION AND MAINTENANCE

The maturation period of a tooth is the era about which we know the least There are several demonstrations in the literature that the caries susceptibility of the molar teeth of rodents decreases as the tooth age increases [84–86] There are also clinical suggestions that if a tooth is protected from decay during its early months in the oral cavity, it attains a greater degree of caries-resistance and is less liable to be attacked by the carious process at later stages These findings suggest a change in tooth structure or in permeability of the tooth after emergence into the oral cavity

Studies with radioisotopes show that the recently erupted tooth has a high ability to incorporate inorganic ions into its structure The rate at which this occurs is between 10 to 20 times faster than the rate of exchange in teeth that have been in the oral cavity for appreciably longer periods of time [87] In addition, the rate of exchange in recently erupted teeth is only about one-half the rate in developing crowns of teeth within the jaw This small difference between unerupted and recently erupted teeth is in striking contrast to the concept that the enamel of erupted teeth is an inert region Further radioisotope studies have shown that the inorganic components incorporated during maturation and during the maintenance period have their origin in the salivary secretions

Another influence upon the maturation of teeth has been demonstrated in histologic studies. The teeth of rats that were exposed to a cariogenic diet during the early post-eruptive period had enamel that was much more permeable to histological stains than comparable teeth in animals which were fed their entire ration by stomach tube.[?] These changes that take place during tooth maturation are influenced by the salivary secretions. In an experiment to study this relationship, rats were desalivated at various intervals after weaning.[88] The subjects in the several groups were maintained on a non-cariogenic diet until the rats in the last group were desalivated. Then all subjects were transferred on the same day to a cariogenic diet on which they were maintained for the same length of time. Under these circumstances the rats which were desalivated at weaning had the highest incidence of carious lesions; their littermates which were desalivated after tooth maturation was complete had significantly less tooth decay. The mechanism by which this influence takes place is not known. Furthermore, we do not know whether variations in the composition of the saliva, nor in the quantity of the saliva may alter the rate or extent of maturation. This relationship between saliva, maturation of teeth and their caries susceptibility indicates a type of metabolic situation that could be altered by an adverse nutritional influence on the quantity or the quality of the saliva.

One of the most interesting areas for exploration in the dental caries field is the relation of systemic nutritional influences upon the teeth after their development and maturation are complete. Of this aspect we know very little and yet there are some recent experiments that suggest the definite importance of nutrition during the maintenance period. In post-developmental studies reported by Haldi and co-workers two diets that were very similar in their carbohydrate, protein and fat composition caused considerably different caries rates in the same strain of animals.[89] Uniformly, rats fed one of these purified diets had a much greater caries incidence than littermate rats fed the other purified diet. This post-developmental influence can be explained only on the basis of the operation of some systemic mechanism that is presently not understood. Since the composition and concentration of the three major components of the two diets were similar, this systemic influence must have been mediated by one or more of the several minor differences in the concentration of the minerals and the vitamins in the two diets. This influence may not have operated primarily through the teeth themselves but possibly through the saliva or some other unrecognized pathway. In the latest study in this series the investigators have reported that the salt mixture used in the less cariogenic of the two diets was capable of reducing the cariogenicity of the other diet when used in place of the other salt mixture.[90]

Another investigation conducted during the post-developmental period was described by Nizel and Harris in hamsters.[91] Subjects fed a diet composed of corn, grown in New England and whole milk powder prepared from milk produced in New England had a high dental caries incidence. Comparable hamsters fed a diet composed of corn and whole milk powder produced in Texas had a significantly lower dental caries incidence. On the basis of chemical analyses, the New England and Texas diets had com-

parable carbohydrate, fat and protein contents, yet on this post developmental basis, strikingly different caries experiences were produced by the two diets

A third experiment of this general nature with equally striking results has been published by McClure and Folk.[9] When skim milk powders were heated mildly, appreciable increases in their caries producing properties for rats were observed Again the carbohydrate, fat and protein percentages were identical before and after the heating process for each skim milk powder tested Further studies have shown that these diets did not contain adequate amounts of lysine When these diets and various heated cereal diets which were also inadequate in lysine were supplemented with lysine, sharp reductions in dental caries on the smooth surfaces were noted[53,93] Supplementation of the diet with lysine was more effective than intubation[93]

A fourth series of experiments has been reported by Constant *et al*,[86,94] in which the influence of various mineral supplements to low mineral, highly cariogenic natural diets fed post-developmentally was appraised in cotton rats Supplements of citrate, lactate or acetate salts did not alter the incidence of tooth decay Supplements of calcium carbonate, disodium phosphate and various salt mixtures with or without calcium retarded the rate of development of caries in the erupted teeth These investigators also noted that mature animals were quite resistant to tooth decay when fed the same low mineral diet that caused extensive tooth decay in weanlings Stralfors[5] has noted that the supplementation of cariogenic diets with phosphates caused major reductions in caries in the hamster In addition, McClure[53] has demonstrated that supplementation of diets that cause smooth surface lesions with 1 6 per cent of dibasic sodium phosphate caused striking reductions in dental caries

At present, there is no explanation for the influences observed in these four types of experimental studies However, somewhere in them valuable clues are contained which are needed to explain how and why such post developmental differences influence the initiation and progression of carious lesions Possibly this information may elucidate some of the seeming paradoxes seen in human populations

In clinical investigations it is important as well as difficult, during maturation and maintenance periods to attempt to evaluate the influence of a diet upon the dental caries incidence in terms of its two potential components the oral environment and the systemic interrelationships This evaluation is especially difficult in experiments or surveys with human subjects A great variety of surveys has been conducted to determine the incidence of dental caries among primitive populations and to determine to what extent their dental caries experience has been modified as they came in contact with civilization Among the most definitive of these surveys were the ones in which the incidence of tooth decay in about 3000 primitive and civilized groups of Eskimos in Greenland were studied[95,96] The percentage of Eskimos with tooth decay in East Greenland varied from 4 3 for the males and 4 6 for the females at the isolated native settlements, up to 43 2 and 51 5, respectively, for the Eskimos residing in the neighborhood of trading stations On the west side of

Greenland, the incidence was much higher and varied from 31 8 per cent for the males and 44 4 per cent for the females in native settlements up to 83 3 and 90 5 per cent respectively for those Eskimos who resided in the immediate neighborhood of the trading posts It has been estimated that an average of 63 per cent of the total dietary intake of the western Greenlanders in 1930 was made up of imported foods especially sugar and cereals instead of the 17 per cent in 1901 In East Greenland the natives in isolated settlements received relatively no imported food, and those at the trading stations, a great deal less than their contemporaries on the western side of the island The data from this survey and numerous others point to the fact that the increasing use of foods associated with civilization has resulted in increased dental caries incidences among the populations using these diets This increase has been widely interpreted to be mediated through changes in the oral environment This may be true in the case of those who have adopted civilized foods after tooth development is complete However in the children of these areas the consumption of the more refined foods during periods of tooth development probably has resulted in the formation of teeth that have a much higher caries-susceptibility than the teeth of their ancestors In addition the teeth of the youngsters erupt into oral environments that are more cariogenic

Numerous experiments have been conducted on the effect of the type and composition of the diet for children on their dental caries experience in attempts to explore in specific terms why such remarkably large differences occur between the caries index of different population groups as described in the Greenland survey above One of the longest series of studies was that conducted by Boyd and co workers at the State University of Iowa who became interested in this problem in the course of their studies on the dietary control of diabetic children[97, 98] These workers reported that where careful dietary control was maintained by the use of diets which were high in fat and protein and low in carbohydrates with ample supplies of all basic nutrients there was much less tooth decay than in children of the same area who were not under such dietary regimentation Many of their cases were studied for prolonged periods of time These workers noted that non adherence to the dietary recommendations resulted within a few months in an increased incidence of tooth decay They believed that the low incidence of tooth decay which they observed in their diabetic children under dietary supervision was due to the general nutritional adequacy of the diet and not to the control of the diabetic process itself

Similar studies were conducted by Drain and Boyd[99] and by McBeath[100, 101] in children in other institutions for normal youngsters When the customary diets were supplemented with milk butter and eggs in the first case, and milk eggs wheat, meat vegetables, oranges butter and cod liver oil in the second case they observed substantial reductions in the incidence of new cavities In studies with out patients Howe and co workers[102, 103] and Livermore[104] reported a lower number of new carious lesions in the patients who were cooperative in accepting and following the recommendations made to them, but observed no reductions in uncooperative patients

The general conclusions of these investigators implicated the nutritional improvement of the diets as the important factor in the causation of the

reduced dental caries increments They believed that the change in the oral environment occasioned by the relatively low carbohydrate content of their diets was less important than the improvement in their nutritional adequacy

Other workers approached this subject from a different point of attack by the addition of various amounts of carbohydrate to the diets of institutionalized children without any attempt to maintain diets of comparable nutritional acceptance[105,106] In one survey conducted in an orphanage, the incidence of tooth decay at the beginning of the experiment was very low, even though the amount of several nutrients in the diet was far below levels considered to be adequate In the case of 51 orphanage children who received approximately 3 pounds of candy per week, definitely increased annual increments of tooth decay were observed during this period of high carbohydrate ingestion Unquestionably, the nutritional adequacy of the diet decreased by reason of the very large amount of candy provided for each child At the same time, the oral environment must have contained a higher amount of readily fermentable carbohydrates during the period of carbohydrate administration than was the case prior to the experiment

In experiments of either of the above two types, there is no practical way in which the degree of influence of the oral and systemic factors can be eliminated, one from another, on the basis of the most detailed published data This is largely true because strict precautions were not taken to hold constant other factors than those under investigation This comment obviously does not question the reliability of the results nor the efficacy of the procedures described for the control of dental caries The probable conclusion that should be drawn from the two series of experiments is that both systemic conditions and the oral environment were influenced by the dietary changes Hence, the altered initiation and development of carious lesions were the end product of changes in the two interrelated facets of the problem However, from the results of the animal studies reviewed above, as well as from controlled clinical studies such as those at Vipeholm Sweden,[13] there can be no question but that the excessive consumption of carbohydrate-containing foods, especially those that are retained on the tooth surfaces, is responsible to a large degree for a high dental caries incidence in caries-susceptible populations

LESIONS OF THE ORAL MUCOUS MEMBRANES AND OF THE SUPPORTING STRUCTURES OF THE TEETH

In the diagnosis and treatment of the various diseases of the oral mucous membranes, and of the supporting tissues of the teeth, it is advisable for the diagnostician to make thorough evaluations of the patient with respect to any oral conditions that may traumatize the surrounding tissues and also to systemic conditions, nutritional, infectious, endocrine, constitutional and psychological, that may predispose to a low tissue resistance As one phase of the systemic evaluation, thorough visual inspection should be made of the tongue, lips, eyes, skin, etc , for any of the classical signs of nutritional deficiency syndromes The various criteria of these syndromes have been described in detail in the particular chapters of this book per

taining to the specific deficiencies When none of these signs are found to exist as indications of frank deficiencies evidence of subclinical dietary deficiency should be sought through discussions with the patient about his diet and also by laboratory tests and whatever clinical methods of evaluation that are applicable in each individual case Frequently such subclinical deficiencies may predispose to a sufficiently low tissue tone and resistance to traumatic or infectious processes that ordinarily tolerable oral conditions become overwhelming in their impact



FIG 44 —Note large ulcerated region on buccal mucosa opposite the left first and second molars at the occlusal level Smears of this area showed heavy concentrations of micro-organisms of the fusospirochetal group Extensive local treatment of the lesion had been ineffective A dietary evaluation suggested a subclinical niacin deficiency (Courtesy of Dr David Weisberger)

An example of the result of such a subclinical deficiency is shown in Figure 44 where a large ulcerated region is seen to exist on the buccal mucosa adjacent to the left molar teeth Smears from this area were heavily laden with micro-organisms of the fusospirochetal group This patient was treated by a variety of local procedures for an appreciable length of time without any noticeable regression in the ulcerated area Then a thorough evaluation of his dietary background suggested that he was likely to be in a state of subclinical deficiency in niacin, but there was no evidence of any of the classical signs of niacin deficiency Hence niacin therapy was begun at a level of 100 mg per day with a quick resolution of the lesion being observed Ninety six hours after the beginning of this therapy the lesion was completely resolved (Fig 45) It will also be noted from this figure that the broken molars that were traumatizing the mucosa in that region had not been repaired This is an example of a traumatic



Fig 45 Same patient as in figure 44, ninety six hours after oral administration of niacin at rate of 100 mg per day No oral treatment was undertaken during this period Note that the traumatic influences of badly broken down molars in the upper and lower quadrants adjacent to previous site of lesion have not been altered (Courtesy of Dr David Weisberger)

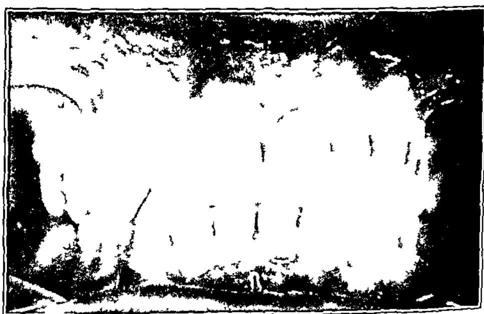


Fig 46 —An ideal example of healthy gingivæ Note the sharply pointed inter dental papillæ and the general appearance arrangement and contours of the gingivæ (Courtesy of Dr Paul Goldhaber)

influence in the oral cavity that precipitated a specific localized lesion by reason of an underlying systemic problem It is doubtful if the state of subclinical niacin deficiency in this patient was sufficiently severe to have resulted in any oral manifestations had it not been for the traumatic conditions imposed by the broken down molars

There is an increasing concern among oral clinicians that many low grade abnormalities of the oral tissues are being dismissed as "normal" because of the frequency of their occurrence The optimal goals to strive for are tissues that are healthy rather than any less satisfactory condition even though the latter is much more commonly observed in the population seen by an oral

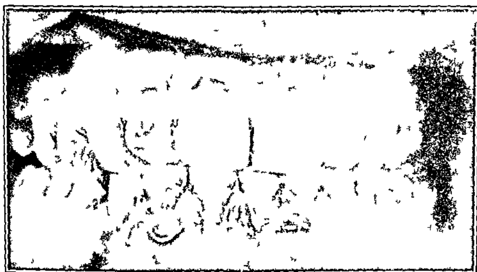


FIG 47 —Ulcerous gingivitis *Note the varying degrees of destruction of the inter*dental papillæ from a slight rolling of the margins and a blunting of the tip of the papilla between the lower central incisors slight necrosis on the papilla between the right central and lateral incisors and gross ulceration of the papillæ between the right lateral incisor and canine and between the left central and lateral incisors (Courtesy of Dr Paul Goldhaber)

clinician An ideal example of healthy gingivae in all respects is shown in figure 46 where the fine pointed interdental papillae are clearly visible and the general position and arrangement of the gingivae and gums with their blood vascular pattern can be discerned This is an ideal objective to compete for but is one that is too rarely seen or achieved by treatment in clinical practice

Gingivitis —Gingivitis is an inflammation of the gingivae including the interdental papillæ There are three main types of gingivitis (1) hemorrhagic gingivitis, (2) ulcerous gingivitis and (3) hypertrophic gingivitis

1 *Hemorrhagic Gingivitis* —Hemorrhagic gingivitis is characterized by free bleeding red gingivæ and edematous interdental papillæ The epithelial lining of the gingival trough is thin and edematous and is usually infiltrated with polymorphonuclear leukocytes Bordering the 'trough epithelium, numerous bacteria and fungi are found The direct cause of

hemorrhagic gingivitis appears to be poor oral hygiene and inadequate dental care where calculus is allowed to collect on the teeth and where broken down teeth, malformations, improperly placed fillings, and traumatic occlusion act as physically debilitating circumstances or as food traps A predisposing systemic cause of hemorrhagic gingivitis occasionally appears to be avitaminosis C, although there unquestionably must be additional factors that are not presently recognized

2 *Ulcerous Gingivitis (Trench Mouth, Vincent s Gingivitis)* —This is an acute and painful condition that is characterized by the loss of the interdental papillæ (Figs 47 and 48), pseudomembrane formation, bad breath regional lymph node involvement, mild lymphocytosis (although not always), some rise in temperature, and anorexia It is particularly characteristic that the first site of attack is the interdental papillæ and that all are not attacked simultaneously Instead, a variety of stages is noted with some papillæ being very slightly involved and others, often close at hand, being completely destroyed (Fig 48) When the process is allowed to go on without interruption, extensive loss of the interdental papillæ is noted with the formation of cup-like ulcers between the teeth (Fig 49) These ulcers are covered with a grayish pseudomembrane formed by the necrotic superficial cells and fibrin Enmeshed in this slough are the micro-organisms of the fusospirochetal group The lesion is characteristically sensitive to any pressure or instrumentation The rest of the gingiva is uniformly inflamed, and it usually appears clinically as a reddened zone rather sharply demarcated from the subjacent gum tissue It is believed that the direct cause of this condition is the fusospirochetal



Fig 48 —Ulcerous gingivitis A more advanced case with extensive necrosis and ulceration of the gingivæ throughout the anterior mandibular region and with a lesser amount of involvement but still relatively advanced effects on the maxillary gingivæ (Courtesy of Dr Paul Goldhaber)



Fig 49 —Hypertrophic gingivitis The chief complaint of this patient was sore gums There was a prolonged history of toothache of a lower left molar necessitating chewing only on the right side Examination revealed diffuse hypertrophic gingivitis localized on the left side of the mouth (Courtesy of Dr David Weisberger)

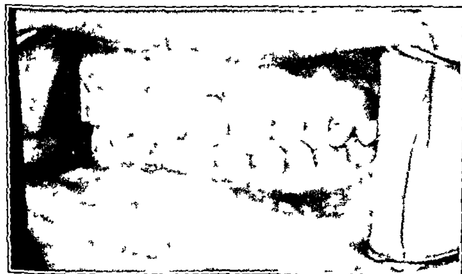


Fig 50 —Same patient as in Figure 49 after treatment that consisted of the removal of caries and filling of the cavity in the molar and active stimulation of the gingiva by chewing wax 3 times daily (Courtesy of Dr David Weisberger)

group of micro-organisms A variety of postulates has been made about underlying causes that predispose toward this rapidly fulminating disease entity Deficiencies of vitamin A and of the B complex have been suspected especially frequently[107] These have not been characterized in sufficient detail to justify any sound working postulate The most satisfactory treatment appears to be a thorough combination of local treatment with adequate diet and the alleviation of any psychological stress or constitutional disorder that may be superimposed upon the condition

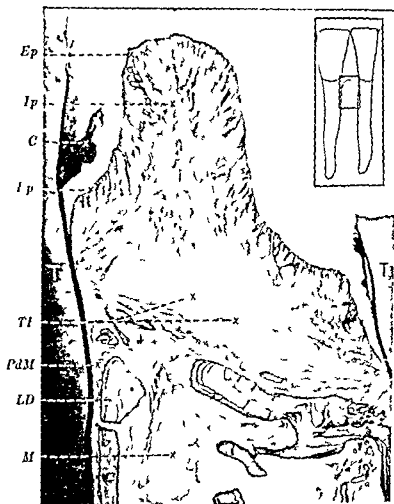


FIG 51 —Normal tissues between two teeth taken from area shown in insert *Ep* epithelium of the interdental papilla (*Ip*) and *Ep* epithelium in gingival crevice *TF* transceptal fibers which join the teeth together (*T I*), *LD* lamina dura and crest of alveolar bone, *M*, marrow, *PdM* periodontal membrane Even though salivary calculus (*C*) is present it has caused no inflammation

3 *Hypertrophic Gingivitis* —This condition may exist either in the acute or in the chronic form Acute hypertrophy of the gingivae is caused by a rapid influx into the gingivae of inflammatory cells, hemorrhage, or abnormal white blood cells When confronted with the acute form of the disease, there is a necessity to think of, and to rule out wherever possible, an acute inflammation, scurvy, purpura, or leukemia It is noteworthy that acute

hypertrophic gingivitis is relatively rare Chronic hypertrophy of the gingivæ is fairly common A wide variety of postulates has been advanced as to the causes These include various forms of vitamin B complex deficiency At least one factor that is involved in the causation of hypertrophic gingivitis is the lack of function In Figures 49 and 50 are demonstrated a case of this syndrome before and after treatment At the first

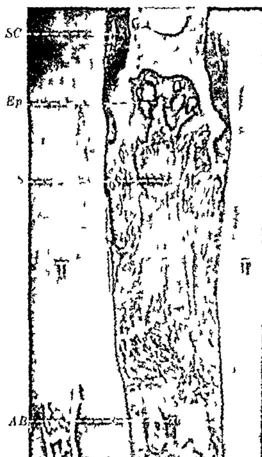


FIG 52 – Pathologic tissue taken from an area similar to that in Figure 51 Periodontoclasia resulting in destruction of the epithelium (*Ep*) severe inflammation of the stroma (*S*) and resorption of alveolar bone (*AB*) *SC* salivary calculus, *T T* two adjoining teeth

examination of the patient a toothache in a lower left molar was recorded and for the previous ten months the patient had been chewing only on the right side Examination revealed that the diffuse hypertrophic gingivitis was localized entirely on the left side of the mouth and that there was a deep carious lesion in the lower left first molar Treatment consisted of removal of the caries filling of the first molar active stimulation of the left gingivæ by having the patient chew wax 3 times a day In Figure 50 the rapid return of the gingivæ to normal size is recorded

Periodontoclasia.—The commonest type of periodontoclasia is that familiarly known as pyorrhea alveolaris. This is in reality a rarefying osteitis of the supporting bone of the teeth and is accompanied by pocket formations that sometimes become infected with the evolution of a considerable amount of pus. Local infection commonly plays an important role in the clinical course of the disease. In order for there to be an infection in these areas, bacteria must pass two barriers of defense in order to form pockets in the alveolar bone (Fig. 51): first, the normal epithelial lining (Ep) of the gingival crevice; second, the strong transverse fibers (TF) over the crest of the alveolus. The latter appear to resist invasion, even after the gingivae have been destroyed. Figure 52 shows a case of periodontoclasia in which the epithelial papilla (Ep′) had degenerated. The stroma (S) is inflamed and complete destruction of the transverse fibers has been achieved.

Local predisposing factors such as calculus formation, food impaction, overhanging margins of tooth restorations and traumatic occlusion apparently are of considerable importance in that they weaken tissue resistance to permit bacterial action to become more active. Although relatively little is known about the nature of systemic predisposing factors, it is likely that one or more systemic factors of nutritional and constitutional nature predispose toward the destruction of the tissues in this area. The main reason for believing in systemic influence of a presently unidentifiable nature is the observation that even after local conditions have been cleared up, periodontoclasia may continue to progress or may not regress. Various postulates concerning low-calcium intake, poor calcium utilization, avitaminoses C and D, and deficiencies of the B complex and endocrine malfunction have been made. However, there is little definite evidence to support any of these hypotheses.

In experimental animals the only deficiency disease which has been reported to be comparable to periodontoclasia is scurvy in the guinea pig in which Boyle and co-workers reported that prolonged vitamin C deficiency resulted in an absorption of the alveolar bone in a way that was characteristic of periodontoclasia in man.[31] However, clinical trials with human patients who had various degrees of periodontoclasia have not uniformly responded to vitamin C therapy, even though the tissues were saturated with vitamin C by administering doses of from 200 to 500 mg. of ascorbic acid daily.

The only studies concerning vitamin D deficiency in relation to osteomalacia and to periodontoclasia have been ones reported from Indian surveys by Taylor and Day.[108] They examined 22 Indian women who were suffering from clinical osteomalacia by reason of diets deficient in calcium and in vitamin D, and found that 11 of them had severe cases of periodontoclasia. In view of the very high incidence of periodontal diseases of all types in India, it is questionable whether the high incidence of periodontoclasia amongst these women with osteomalacia was attributable to the osteomalacia or was simply a manifestation that would have been expected in any group of Indian women of comparable age. However, more thorough clinical studies in this area are badly needed to provide definite information.

In the dog and in the monkey, various experiments in which B complex deficiencies were produced with resultant effects upon gingival inflammation and infection have been reported. Becks and Morgan described deficiencies in the filtrate faction of the vitamin B complex, most likely pantothenic acid deficiency, and niacin deficiency in which severe abnormalities were reported in the supporting structures of the teeth of dogs.[109] Likewise, in monkeys fed diets deficient in the B complex Chapman and Harris have produced severe gangrenous lesions of the gingival tissue and osteitis of the alveolar bone with exfoliation of the teeth.[110] These observations suggest that there are predisposing nutritional factors when the deficiencies are particularly severe to produce clinical entities comparable in some degrees to periodontal destruction. However, comparable observations are not available in human surveys.

For the best treatment of periodontoclasia local irritating factors must be removed by proper procedures. The most satisfactory benefit from local treatment will be achieved when there is an accompanying improvement in systemic conditions. Though there are no specific dietary entities which have been clearly shown to be related to clinical periodontoclasia, improvement of the diet in all regards is strongly indicated. The best dietary prescription which can be given in these cases is the adherence to a fully adequate diet in all regards. Where there is reason to believe that one or more specific deficiencies exist in the patient, suitable therapeutic preparations should be given. Where there is no indication of specific deficiencies, general improvement of the diet will be found adequate without supplementation by proprietary materials.

Relationships of Chewing Ability and Nutriture.—Examples of an interrelationship between proper dentures and malnutrition have been reported. Mann and co-workers made a clinical study of 160 edentulous patients with a long-standing clinical record of multiple deficiency disease who had been under their observation for at least three years.[111] All had previous histories or present evidence of chronic pellagra, beriberi, scurvy, or riboflavin deficiency. The identity of these deficiencies was established by the presence of characteristic mucosal membrane lesions of pellagra, of the nutritional peripheral neuritis of beriberi, of the gingival lesions of scurvy, and of angular cheilosis and the ocular lesions of riboflavin deficiency.

The vertical dimension of the face had decreased in 140 out of the 160 cases. Fifty-seven of the 74 patients who had only 1 denture, or none, had perleche. Fifty-two of the 66 patients who were wearing dentures with decreased vertical dimension gave evidence of perleche. In contrast, only 7 of the 20 cases with a normal vertical dimension showed any evidence of angular cheilosis. Ninety-eight of the patients with a reduced vertical dimension complained of symptoms arising from the alimentary tract (burning of the mouth and tongue, epigastric burning and pain, nausea and vomiting, intermittent diarrhea, cramping and anorexia). Only 8 of the 20 patients with a normal vertical dimension mentioned these subjective symptoms. In the majority of these patients artificial dentures had been constructed poorly or of inferior materials. This resulted in much irritation that was ultimately augmented by the unsanitary condition of these appliances. Under these circumstances in many of these patients,

the consumption of adequate amounts of an adequate variety of foodstuffs was either difficult or impossible When patients with a reduced vertical dimension were given riboflavin, there was a reduction in the cheilotic lesions, but at no time did these lesions disappear if a reduced vertical dimension was still present Niacin and pyridoxine did not have any effect on angular cheilosis, although they aided in the reduction of other symptoms characteristic of these particular deficiencies

These data indicate the necessity to restore adequate dental function by well-fitted dentures that restore the normal vertical dimension Even dentures that are perfect when originally fitted must be examined periodically to determine whether or not the alveolar ridges have been resorbed sufficiently to alter the original normal relationships If such a reduction in dental function is allowed to persist, perleche may result from the decreased vertical dimension of the face and a complex nutritional deficiency disease may arise from the inability to masticate an adequate amount of food or an adequate variety of food

In a continuation of these studies Greene and co-workers made a survey of the incidence of impaired mastication ability in 446 consecutive patients at the Nutrition Clinic of the Hillman Hospital in Birmingham Alabama Masticatory insufficiency was the term that was used to describe a variable clinical condition that resulted from one reason or another in the inadequate ability to chew food A patient was considered to be in the state of masticatory insufficiency if any one of the following conditions prevailed (1) no natural teeth and artificial dentures that were inadequate or painfully fitting, (2) no natural teeth and no artificial dentures or only one denture or (3) less than 3 opposing serviceable natural masticating teeth and 3 opposing serviceable natural anterior teeth and no functional replacements in the form of dentures or bridges Two hundred and sixty eight of these patients had no natural teeth Only 49 of these edentulous individuals had well-balanced functional artificial dentures Of the 178 individuals who still had some natural teeth only 96 had well balanced dentitions Thus, 301 of the 446 patients had various degrees of masticatory insufficiency, and only 145 had natural or artificial well functioning dentitions according to the definitions laid down by the investigators The incidence of masticatory insufficiency was observed to increase appreciably with age

A further problem with patients who have been edentulous for prolonged periods is the difficulty in designing and making dentures that are comfortable and masticatorily efficient After prolonged periods of edentulousness the mucous membranes of the mouth and lips are sufficiently atrophied and altered that the wearing of plates is very difficult In these cases in particular there is a special necessity to correct the underlying nutritional disorders that have arisen over the edentulous period Otherwise successful construction and fitting of the dentures in tissues with reduced viability and altered structure will increase the likelihood of unsatisfactory results

Leukoplakia —Leukoplakia is a group term used to designate a number of histologically dissimilar conditions The chief clinical characteristic is a whitish surface on the oral mucosa This may vary from an opalescent silvery sheen, where the mucous membrane looks as if it had been painted

with silver nitrate, as shown in Figure 53, to thick corrugated leathery patches, as shown in Figures 54 and 55 The condition may occur in patches, with the dorsum of the tongue being the commonest site for this variety or in lines as seen most frequently on the inside of the cheek and occasionally on the gums and the tongue Leukoplakia is generally considered to be a precancerous lesion The histological appearance of leukoplakia may be either epithelial hyperplasia or a hyperkeratosis The epithelial hyperplastic lesion is chiefly seen on the tongue It ordinarily begins as a smooth area of epithelial atrophy that later as the epithelial cells hyperplastically regenerate changes to a white raised, roughened



Fig 53 —Leukoplakia on the middle third of the lateral margin of the tongue Note opalescent silvery sheen of the mucous membrane resembling an area that had been treated with applications of silver nitrate (*Courtesy of Dr David Weisberger*)

patch Histologically the epithelium is markedly hyperplastic and the upper layers instead of being cornified are vacuolated and show hydropic change The hyperkeratotic lesions are characterized by a dense, raised white patch that may be localized or quite extensive The chief histological characteristics are the marked increase in the thickness of the corneous layer and the increase in the number of keratohyaline granules of the stratum granulosum The remainder of the epithelium may be atrophied Occasionally it is hyperplastic A typical instance is on the buccal gum of the right maxilla in which the palate was also involved (Fig 56)

Lichen planus is an inflammatory mildly keratotic lesion Clinically it appears as thin silvery striae and occasionally as small thin patches The lesions are found on the inside of the cheek on the buccal gum and on the tongue Often there are accompanying skin lesions

Fig 54 —Leukoplakia on dorsum of tongue in large relatively smooth leathery patches *stretching along either side of tongue from near the base to the anterior third* (Courtesy of Dr David Weisberger)



Fig 55 —Leukoplakia on ventral aspect of tongue in heavy corrugated leather patches (Courtesy of Dr David Weisberger)

In all three of these conditions, epithelial hyperplasia, hyperkeratosis and lichen planus various suggestions have been made that there are nutritional involvements of either vitamin A or vitamin B complex deficiency, although there is no clear-cut demonstration of predisposition by any of these conditions In addition, local irritants trauma tobacco, etc, have been postulated as causative factors Definite evidence to support a traumatic entity is often lacking in patients

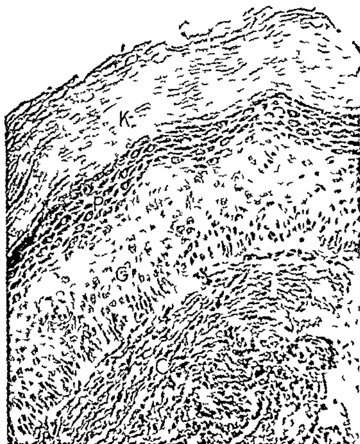


FIG 56 —The histology of the lesion shown in Figure 55 The keratin layer (K) is very broad and the stratum granulosum (G) has been widened and accentuated The prickle cell layer (P) is atrophied and the rete pegs are blunted There is no inflammation in the corium (C) (Cahn L R Pathology of the Oral Cavity Baltimore The Williams & Wilkins Co 1941)

Xerostomia —This is an extremely rare condition that is believed to be induced by a prolonged avitaminosis A in a comparable fashion to that in which xerophthalmia is induced In animals, besides atrophy of the lacrimal glands occlusion of the main ducts of the salivary glands by desquamated epithelium has been observed In human cases with completely dry cornea, there has been reported a lack of salivary secretion and thickened, whitish mucous membranes of the mouth These symptoms al disappear after administration of large doses of vitamin A However it

should be pointed out that this is an extremely rare condition in human beings in the United States

Pain —Oral pain may vary from the annoyance of a "burning" sensation in the tongue to the excruciating manifestations of "tic douloureux" The 'burning" tongue is one of the most difficult problems with which the dentist and physician must cope Each case is a diagnostic problem in itself The condition is usually localized in the lateral margins and the tip of the tongue and is described as a peppery feeling or a burning sensation This is commonly an early sign of pernicious anemia, and also occurs early in pellagra, sometimes in diabetes, early pregnancy, and alcoholism In all of these situations a deficiency of one or more members of the vitamin B complex may be involved If the diagnosis of the underlying factor can be made, the 'burning tongue" is easily corrected If there is suspicion of faulty absorption of nutrients, the parenteral route is advisable In all cases, treatment is likely to be prolonged Various claims have been made for specific effects of thiamine chloride and of pyridoxine hydrochloride However there is no data to corroborate these statements with any degree of accuracy, although isolated cases may have responded to therapy in this line From available data, it cannot be deduced that these are specific for the treatment of such sensations as are described under the terms, 'burning tongue" or "tic douloureux" In these conditions, it is important to remember to treat local conditions that may contribute to the breakdown of the adjacent tissues, but in addition, systemic conditions of a rather general nature must be considered and evaluated It is relatively rare that individual nutrients will be found to be responsible for any of these manifestations

By far the better means of treating dietary abnormalities that may accompany or predispose toward these local lesions of the oral mucous membranes or of the supporting structures of the teeth is the prescription of a well balanced diet composed of the seven basic food categories with a general distribution of the foods generously amongst the several groups In cases where there is clear-cut evidence of prolonged deficiency of one or more nutrients, there is obviously justification that these should be supplied in purified form in high enough amounts to replete the body supplies However, by and large, this is neither necessary nor desirable In addition, where there are cases of faulty absorption or excessive requirements by reason of peculiar constitutional circumstances or accompanying disease requirements, then supplementation also is in order It is noteworthy too, in connection with postoperative healing, especially when there are extensive needs in the oral cavity, that a diet of generously adequate nature with respect to all of the nutrients should be prescribed

SUMMARY

Our knowledge about the relationships of nutrition to the diseases of the oral cavity has been rapidly expanding during the past decade This is best exemplified by the increased factual information about the relationship of nutrition to the development, the maturation and the maintenance of the teeth and to the caries susceptibility of the teeth In so far as the

influence of nutrition upon the lesions of the oral mucous membranes and of the supporting structures of the teeth is concerned, we still have a much smaller collection of established facts than is needed It is not unreasonable to assume by reason of the rapidly expanding horizons in nutritional research that the next decade or two may well provide as many substantial answers to the latter category of oral problems as has been added to our pool of knowledge about tooth decay in the past decade or two It is noteworthy, although not surprising in view of the chronic nature of most oral problems, that many of the nutritional problems of the mouth involve metabolic abnormalities which create predispositions to disease entities to be manifest years or decades later

The best advice for any age group about the dietary regimen that will provide the best opportunity for normal oral tissues is simple and straightforward Each of the basic seven food categories should be represented liberally in each day's diet, and as many as possible in each of the day's three meals The best selection of foods for dental health is one where as many of the foods as possible are purchased in their natural state without excessive refining and where the cooking procedures are such as to conserve the maximum of the original nutritive value Attention should also be paid to the inclusion in the diet of a frequent and varied series of foods that require vigorous mastication as a means to stimulate and exercise the various tissues and organs involved in the comminution of food In addition a liberal source of vitamin D should be provided daily throughout the entire period of an individual's growth and development A minimum of sticky adherent, high-carbohydrate foods with a low rate of clearance from the oral cavity should be consumed After eating foods with a slow oral clearance the teeth should be cleaned thoroughly by the procedure of choice to be recommended by the dentist As in between meal snacks, in place of sticky high carbohydrate foods, fresh fruits vegetables, fruit juices, milk and other dairy products are much to be preferred from a dental health standpoint In the over-all nutritional planning for improved dental health one of the most important facets to be considered is the fluoridation of public water supplies

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Chapter 21

Principles of Dietotherapy

By Michael G Wohl

A sick person as a healthy person should be maintained in nutritional homeostasis To accomplish this the practicing physician should keep in mind four general principles (1) loss of nitrogen due to stress, (2) nutritional deficiencies concomitant with disease must be looked for and cleared up, (3) the therapeutic diet is a modified normal diet, and (4) the therapeutic diet must be psychologically acceptable to the patient

Loss of Nitrogen Due to Stress —During stress, either from illness or trauma, there is a great loss of nitrogen Loss of nitrogen may begin a few days to a week after injury or illness and continue for one to two months Thus, a gradual depletion of body protein may ensue Proteins, as is well known, are necessary for repair of tissues They are also essential for transportation of lipids in the body, for maintenance of normal blood volume and total circulating blood mass They provide essential amino acids for the formation of hormones, enzymes, antigens and antibodies Also with loss of nitrogen, there is a loss of potassium Thus loss of protein may cause profound disturbances in the physiologic processes of the body Depletion of body proteins varies with the severity of the illness For instance Grossman and others have shown that in meningococcic meningitis, after the temperature has returned to normal and signs and symptoms of the disease have abated, the patient may still lose nitrogen and show depletion of the body proteins As the patient recovers from his illness, his nitrogen excretion falls and with the higher food intake nitrogen balance may become positive and this will continue until his body proteins are restored It should be borne in mind that to replete the patient, protein intake should be gradual and not too excessive, for excessive amounts of protein may increase blood urea nitrogen to dangerous levels, and in liver disease, blood ammonia may rise and lead to a state indistinguishable from hepatic coma By prescribing an adequate total daily caloric intake, a protein intake of 100 to 150 grams may be sufficient to replete body proteins However, when the total daily calories are inadequate, protein may be deaminized and transformed into carbohydrate to help provide energy Thus, the ordering of a high protein diet without actually knowing the composition of the diet is meaningless

Concomitant Nutritional Deficiencies —A patient may be successfully treated for an organic disease like hyperthyroidism, colitis, peptic ulcer, or anemia and yet continue to exhibit this or that vague unpathognomonic sign or symptom The reason for this is usually that the sign or symptom is caused by an undiagnosed nutritional deficiency concomitant with the

organic disease. One may not realize that during illness there may be a catabolic loss of nitrogen, or interference with digestion, utilization or absorption of one or several nutrient factors, or perhaps an imbalance in the interrelationship between nutrients, or a loss of fluids, electrolytes and vitamins by the way of the gastro-intestinal or renal tracts. This leads to nutritional deficiency. Furthermore, the patient's requirements for essential food factors may be increased by stress of disease, injury, environmental factors or certain drugs and medicinal agents. All these may lead to deficiency of essential food factors in tissue cells. Unless it is corrected, the patient may remain chronically ill even though the underlying disease has been brought under control. From this it follows rather obviously that concomitant nutritional deficiencies often retard convalescence and interfere with total recovery from a disease.

The earliest manifestation of nutritional aberration is a fundamental change in the intracellular chemistry (enzyme system) resulting in altered tissue physiology. Later structural derangement occurs and certain anatomical changes and various other objective and subjective signs are likely to appear. Unfortunately, there are at present no adequate nor easily available laboratory or clinical techniques for diagnosing nutritional aberrations at the start, hence such diagnoses must depend on the physician's medical acumen. This being so, the physician will do well, whenever he finds symptoms of apathy, depression, weakness, or loss of appetite in a patient whom he is treating for organic disease, to suspect a concomitant nutritional deficiency. The following conditions are likely to be associated with nutritional deficiency:

1. Conditions that interfere with food intake—anorexia, nausea, vomiting, gastrointestinal disorders, allergy, neurologic disorders, dental troubles.
2. Conditions that interfere with absorption of nutrients—diarrhea, achlorhydria, hepatic and cholecystic disease.
3. Conditions that interfere with utilization of nutrients—hepatic disease, diabetes, alcoholism.
4. Conditions that increase nutritional requirements—unusual activity, fever, hyperthyroidism, pregnancy, lactation.
5. Conditions that increase excretion—sweating, polyuria, dehydration.

Necessary therapy may also interfere with nutrition as the following do: antacids, diuretics, thyroid medication, mineral oils, forced fluids, infusions, oral antibiotics and chemotherapeutic agents.

Therapeutic Diet.—Insofar as possible every special diet should be patterned after the usual diet, consist of customary foods, adapted to the patient's food preferences, and keep the patient in nutritional homeostasis. Indeed, the therapeutic diet is merely a normal diet quantitatively and qualitatively modified (in consistency, flavor, digestibility or manner of service and preparation) to combat a specific physiopathologic process.*

The oral route of feeding is the method of choice and has the advantages of ease of administration, cheapness and greater efficiency. When the

*To improve the flavor and acceptability of therapeutic diets one may use in moderation spices, herbs and other flavorings as lemon juice, vinegar, vanilla, saccharin, cyclamate (Sucaryl), onion and garlic. Publ. 325 N. A. Sci. N. R. Council, July, 1954.

patient will not eat or drink sufficiently, tube feeding or parenteral administration may become necessary Before resorting to intravenous feeding, tube feeding is to be tried

Psychologic Factors —In prescribing a special diet, the physician must consider the patient as a whole personality—his emotional, economic and social status The patient should find the diet psychologically acceptable and be able to follow it at home The physician should consider, further, that anyone subjected for any length of time to a special diet is apt to suffer certain personality changes, to feel "different" perhaps, to feel that, since he is not like other people in this respect, he is not like them in others and cannot compete with them If the special-diet patient of this sort is a child, he is likely to become a problem child Hence when the physician has a special-diet child on his hands, he should take that small patient off the special diet as soon as possible What is more, the special diet for a child should always be arranged with an eye to making the child as little conspicuous, as little "different" from his playmates as possible Nowdays no physician can decently prescribe a diet and ignore the patient's psychology

Status of Dietitian —The dietitian forms an indispensable link in the triangle—physician, patient, and dietitian It is the function of the physician to base his patient's nutritional program on that patient's underlying pathologic physiology He should apprise the dietitian of the special problems involved in the management of the patient Indeed, it is desirable wherever feasible, to have the dietitian join the doctor on his medical rounds and so become acquainted with each patient and learn at first hand his dietary needs By virtue of her special training the dietitian may often make valuable suggestions The physician should also explain to the patient the reason for this or that particular diet and the necessity for adhering to it The dietitian will use her special talents to devise diets that are attractive and acceptable to the patient, yet remain within the limitations involved

BASIC DIET

In planning a therapeutic diet, it is useful to follow a normal diet It is to be emphasized that a therapeutic diet is built upon the same basic foods required for adequate nutrition of a normal person The diet is arranged in food groups so that the patient can select the kind of food items he prefers in each category of meat, fish, cereals, bread, vegetables citrus fruits, etc (*See* Appendix)

To illustrate, let us suppose that a low calorie diet is desired Reference to the Basic Diet in Table 57 makes it evident that a nutritionally adequate diet can be planned by using one or more of the following simple modifications depending on the desired calorie level (*a*) use skim milk and decrease the butter or margarine, (*b*) reduce the amounts of bread, cereal, and/or potato but use whole milk, (*c*) include 1 to 2 extra servings of vegetables and fruit in order to provide extra bulk, better meal acceptability, and replacement of vitamins and minerals which are decreased by the reduced amounts of breads and cereals

Again, what problems of nutritive adequacy would be encountered if a

TABLE 57.—NUTRITIVE VALUE OF BASIC DIET[2]

Food	Measure	Weight	Calories[1]	Protein[1]	Fat[1]	Carbohydrate[1]	Ca	Fe	Vitamin A	Vitamin Ascorbic acid	Vitamin Thiamine	Vitamin Riboflavin	Vitamin Niacin
		Gm		Gm	Gm	Gm	Gm	mg	I.U.	mg	mg	mg	mg
Milk or equivalent	3 cups	720	480	26	27	36	0.84	0.7	1,230	6	0.30	1.29	0.9
Meat, fish, or fowl[2]	3 ounces (raw wt.)	75 (cooked)	160	17	10	1	0.01	2.8	1,495	1	0.23	0.24	3.8
Egg	1	50	80	7	6	—	0.03	1.4	495	—	0.07	0.18	—
Other protein[3]	1 serving	50	90	6	6	3	0.05	1.1	205	—	0.08	0.11	0.4
Whole-grain or enriched bread	1 serving	30 (dry)	80	2	1	15	0.01	0.6	—	—	0.06	0.04	0.6
Whole-grain or enriched bread	3 slices	90	240	8	3	45	0.03	1.8	—	—	0.18	0.12	1.8
Potato	1–2 servings[4]	150	130	3	—	29	0.02	1.1	50	12	0.12	0.05	1.5
Green or yellow vegetable	1–2 servings[4]	150	50	3	—	10	0.14	2.1	6,225	44	0.13	0.22	0.9
Other vegetable	1 serving	100	30	1	—	7	0.03	0.5	265	14	0.03	0.03	0.3
Citrus fruit	1 serving	100	50	1	—	11	0.02	0.4	180	42	0.07	0.03	0.2
Other fruit	1 serving	100	55	1	—	13	0.01	0.4	740	11	0.03	0.04	0.3
Butter or fortified margarine	2 tablespoons	30	210	—	24	—	—	—	960	—	—	—	—
			1655	75	77	170	1.19	12.9	11,845	130	1.30	2.35	10.7[5]
Recommended Dietary Allowances[6] (1958 Revision)	Women		2200	58	—	—	0.8	12	5,000	70	1.1	1.5	17
	Men		3000	70	—	—	0.8	10	5,000	75	1.5	1.8	20

[1]Calories have been rounded off to the nearest 5 and protein, fat and carbohydrate to the nearest whole gram. In computing the averages for fruits and vegetables, the values have been weighted to conform roughly to the available food supplies.

[2]This assumes per two-week period: beef, veal, lamb, fowl—525 Gm.; pork, ham—300 Gm.; fish—150 Gm.; liver—75 Gm.

[3]Average of foods used for luncheon and supper dishes. Includes cheese, legumes, additional meat or egg—small serving.

[4]It is assumed that 1–2 servings of potato and of green leafy or yellow vegetables will average 150 Gm. per day.

[5]The liberal tryptophan content of this diet together with this level of niacin will amply fill the niacin requirement.

[6]45 years of age, Men: weight, 154 lb.; height, 69 inches.
45 years of age, Women: weight, 128 lb.; height, 64 inches.

We are indebted to Dr. Corinne Robinson for permission to use this Table and material quoted from "Practical Diet Therapy," published by The American Journal of Clinical Nutrition, Inc., 1955.

dietary program required the entire omission of milk? With the use of the calculated foundation diet it quickly becomes evident that milk contributes outstandingly to the protein, calcium, and riboflavin content of the diet, and importantly to the thiamine level of intake Perhaps meat or eggs can be used in greater amounts to compensate for the protein supplied by milk, but these foods are not suitable substitutions with respect to calcium and riboflavin levels of the diet Hard cheese is a desirable substitute for these valuable nutrients of milk but in some situations such as the 200 mg sodium diet it cannot be used The physician then recognizes the need for prescribing supplements if the diet is to be used for more than a few days

If, for example, raw fruits and vegetables are contraindicated in a certain clinical state, the use of all cooked foods may significantly lower the mineral and vitamin contributions of these classes of foods Reference to the Basic Diet makes it apparent that one way to maintain the desirable ascorbic acid intake would be to double the amount of citrus fruit juice

The physician who consistently evaluates the dietary regimens he prescribes in terms of the normal diet will find that his patients accept his recommendations more willingly and are likely to abide by a program which permits individual food choice as well as suitable meal arrangements Dietary modifications are less frequently made, because it is found that the normal diet is, after all, the most effective program in a great variety of situations' (C H Robinson)

Specific diets devised for treatment of disease are outlined in each chapter dealing with the specific pathologic condition The diets represent those used in various hospitals with which the author is connected Although there are some minor differences in the composition of specific diets between hospitals, on the whole, they have been patterned after a normal diet

Acute Febrile Diseases —In patients with minor infections of brief duration, such as acute respiratory infections there is no great disturbance in nitrogen metabolism, hence, maintaining the fluid intake plus whatever food the patient desires is often all that is required If the febrile illness is more serious or of more than a few days in duration, there may be marked nitrogen loss A diet should be provided in which milk and fruit juices are the mainstays and soft boiled eggs, cooked cereals custards and junkets *etc* the supplementary foods As soon as conditions permit and the patient s appetite improves, more and more food containing *high quality protein* carbohydrates fat, minerals and vitamins ("adequate diet") should be added

It should be emphasized that dietotherapy must be *integrated* with antibiotic, chemotherapeutic and other modalities that enter in the total program of patient care

Subacute and Chronic Febrile Diseases —In febrile illness lasting for more than seven days the caloric requirement is large As Shaefer and Coleman have demonstrated typhoid patients can be brought into nitrogen balance with a diet *providing from 3500 to 5000 calories a day, from 70 to* 90 gm of protein and enough carbohydrate to make up the greater part of the energy intake and maintain weight With such a diet mortality is *lessened,* the patient shows marked improvement in well-being loss of weight is greatly curtailed, and convalescence is accelerated

During the first few days of a long febrile illness a liquid diet is usually given As the patient slowly recovers he is given first a soft diet and then an adequate diet without roughage Since Vitamin B complex and Vitamin C needs in febrile illness are higher than normal, the increased vitamin requirement is met by prescribing a high potency vitamin supplement (*See* page 535)

TUBE FEEDING

When the patient's condition is such as to preclude oral ingestion of food, tube or intravenous feeding will have to be resorted to

Indications for Tube Feeding —1 Primary malnutrition without organic cause, *e g* anorexia nervosa

2 Anorexia and vomiting due to organic disease and when prolonged and severe enough to limit nutritional adequacy,

3 Semiconsciousness or coma,

4 Mental disease,

5 Oral pathology, maxillofacial surgery,

6 Paralysis of swallowing muscles

7 Acute and chronic infection severe burns terminal malignancy

Any type of rubber Levin-type tube may be used, however, the smooth thin polyethylene tubing recently introduced, lends itself to gastric as well as nasal passage it is well tolerated and may be left in place without changing up to four months without clogging or producing irritation

Certain precautions are to be taken in tube feeding they are small frequent feedings and aspiration with syringe from stomach of any trapped air This may prevent abdominal distention Development of diarrhea is another complication to be avoided If diarrhea is present the addition of Kaopectate Kanana Banana flake or applesauce may frequently afford effective control

Careful nursing supervision is essential and immediate suction is to be applied in case of regurgitation or aspiration

Composition of Tube Feeding Mixture —The material for naso gastric tube feeding should contain the necessary amounts of protein, carbohydrate fat, minerals and vitamins to meet all the therapeutic needs of the Committee on Therapeutic Nutrition of the National Research Council Types of food which can be used are obtainable in most household kitchens There are available at present special mixtures that can be prepared simply and conveniently The Commission on Nutrition of the Medical Society of the State of Pennsylvania have recently suggested the following formulae for tube feeding *

Intravenous Feeding —Indications for intravenous feeding and composition diet are given in Chapter 32, p 931

Soy Bean Milk —Recently Krehl used a preparation of soya bean milk diluted 1 1 with water and supplemented with vitamins He found it to be a convenient, relatively inexpensive formula for tube feeding It is well tolerated by the patient and produces a minimum of gastrointestinal complications

*Manual of Standard Therapeutic Diets prepared by Commission on Nutrition Michael G Wohl M D , Chairman, The Medical Society of the State of Pennsylvania 1956

No 1		*Grams*	*Calories per fluid o*
Water		1 000	45
Sustagen		500	

Pour the required amount of warm water (120° F) into a vessel of suitable size Add the required quantity of Sustagen to the surface of the water Allow the powder to absorb water Mix until blended and smooth Strain

No 2			
Whole Milk		1,000	30
Meritene		150	

Pour milk into a covered jar, mixer or beater Add Meritene and shake, mix or beat until smooth

No 3			
Whole Milk		1,000	48
Egg Yolks	4 yolks		
Heavy Cream 40%		240	
Karo Syrup		100	
Yeast Two cakes dissolved in 200 cc hot water Mix all together and cook in a double boiler Cool, strain and add orange juice		200	
Cod Liver Oil		16	

No 4			
Water		1 000	38
Powder Skim Milk		225	
Powder Whole Milk		200	

The water in this formula is used to reconstitute the skim milk

APPROXIMATE ANALYSIS

	Calories	*Protein gm*	*Fat gm*	*Cho gm*	*Ca gm*	*Fe mg*	*Vit A I U*	*Ascorbic Acid mg*	*Thiamine mg*	*Riboflavin mg*
Formula 1	2035	118	18	323	3 5	8	2778	167	5 5	5 5
Formula 2	1205	84	40	131	2 6	22	9550	136	3 8	8 1
Formula 3	2321	54	158	183	1 5	7	7270	110	0 9	2 9
Formula 4	1798	132	56	193	4 8	3	2890	28	1 4	7 3
Recommended	3200	65			0 8	12	5000	75	1 6	1 6

Recommended allowances for a 65 Kg 25 year old man, *moderately active* are used comparison

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Chapter 22

A. Nutrition in Diseases of the Stomach

By Burrill B. Crohn and Henry D. Janowitz

Nutrition and the stomach will be discussed under two general headings: 1. The role of the stomach in nutrition, and 2. The role of nutrition and diet in specific diseases of the stomach.

I. THE ROLE OF THE STOMACH IN NUTRITION

Food Intake.—Recent studies have deemphasized the role of the stomach in the phenomena of hunger and appetite. It does appear that the gastric hunger contractions are relatively unimportant in most adults in acting as stimuli for eating. However the upper G. I. tract does regulate in part the volume of food eaten on a meal-to-meal basis. This the stomach accomplishes by means of gastric stretch receptors which respond to distention, and which in turn regulate the rate at which the stomach empties. For reasons which are still obscure, inflammatory or neoplastic lesions of the stomach cause anorexia and consequent nutritional impairment due to restricted food intake.

Gastric Digestion.—Under normal physiologic conditions gastric proteolysis is an integral part of the digestive process. Digestion of carbohydrates by salivary amylase cannot, of course, proceed in an acid medium and gastric lipolysis does not occur to any significant degree. The details of peptic digestion are discussed in Chapter 2, page 44. Here it will suffice that this process results in the degradation of protein to peptones and polypeptides. The ultimate reduction to individual amino acids occurs beyond the pylorus. Yet under certain conditions nutrition may be maintained unimpaired in the complete absence of gastric proteolysis. In the achylia gastrica of Addisonian anemia, a complete lack of acid and pepsin exists, yet nutrition is generally well maintained; contrary to customary teachings constipation rather than diarrhea prevails and weight is undisturbed. However, subtotal gastrectomy for peptic ulcer, which is now in widespread use and markedly increasing in the younger age-group, may constitute a nutritional handicap for some individuals. An increasing number of studies indicate that a significant number of these individuals may either fail to gain weight or continue to lose weight after operation. The clinical studies in patients with total gastrectomy are difficult to interpret since these individuals are usually operated upon for carcinoma. Apparently there is a large "safety factor" in gastric digestion which does not hold for total gastric function including the stomach's activity as a reservoir.

Gastric Absorption.—While some drugs, water and alcohol may be absorbed from the human stomach, gastric absorption of the significant nutrients does not occur.

II THE ROLE OF NUTRITION AND DIET IN SPECIFIC DISEASES OF THE STOMACH

The relation between nutrition and diseases of the stomach is a complex one Diseases of the upper gastrointestinal tract may interfere with the actual intake of food by disturbing the appetite, inducing nausea and vomiting, and producing mechanical obstruction On the other hand, the medical therapy of disorders of the upper gastrointestinal tract is in large part dietetic And, finally, surgical therapy of the stomach may lead to nutritional disturbances requiring correction

Dyspepsia (Gastric Indigestion) —Under this rubric may be lumped together a wide variety of complaints referable to the upper gastrointestinal tract nausea, loss of appetite, belching, heartburn, distention, epigastric distress and pain It is convenient to divide these into two main categories (1) organic dyspepsia, that due directly to organic disease of the upper gastrointestinal tract or reflexly from organic disease elsewhere, (2) functional dyspepsia, it is this category which constitutes the majority of patients seen by the gastroenterologist Of 100 serial cases probably only 30 will be of organic origin, whereas 70 will be of functional origin

Dyspepsia of reflex origin is rather frequent Gallbladder disease, recurrent appendicitis, renal calculus, lead poisoning, diverticulitis and hernia reflexly affect gastric digestion giving rise to pain, heartburn, belching and loss of appetite The attendant reduced dietary intake leads to nutritional loss and diminished body weight The physician must be alert if he is to appreciate this sort of dyspepsia Once he has found it he must remove it by appropriate surgical and medical methods and establish normal food habits

One symptom of functional origin deserves separate consideration This is heartburn, pyrosis or "water brash" Although loosely grouped as a functional complaint in patients who do not have gallbladder or ulcer disease, in a definite number of patients it is clearly due to regurgitation of acid gastric contents into the lower end of the esophagus In these patients careful radiological study usually reveals that the incompetence of the hiatal sphincter is secondary to hiatus hernia

Dyspepsia due to systemic disease is frequent also and again calls upon the physician for skillful diagnosis Hypertension, coronary artery disease, cerebral arteriosclerosis, chronic nephritis, brain tumor, diabetes—these represent a large group of diseases which indirectly affect digestion and lead to loss of appetite, epigastric discomfort and reduced dietary intake and, hence, to a negative balance of food In treatment of this class of dyspepsia the attack is obviously against the primary disease General rules do not hold for this large category of diseases To attempt to treat the gastric indigestion while neglecting the underlying malady is as dangerous as it is futile

Nervous Indigestion —Dyspepsia due to nervous psychiatric or psychoneurotic causes is the kind of dyspepsia most frequently encountered Usually it is chronic and is based upon constitutional nervous inferiority associated psychic disturbances accompanied by insomnia, constipation, and poor appetite Among those who suffer from it are the "constitutionally

inadequate" the truly neurasthenic, the hysterical, and those who have an "irritable colon" or suffer from mucous colitis And there are the psychoneurotic dyspeptics those who are frustrated or have parental or infantile fixations or cannot adapt themselves to family difficulties or the wear and tear the strain and speed of our highly mechanized life those who suffer from 'mother in law complex" "only children" Add to these those who eat badly, rush their meals and overindulge in rich foods, delicatessen dishes and condiments, those who study dietetics with assiduous ignorance, the vegetarians the carnivores, and those who discover themselves "allergic' to fats and it becomes clear how appallingly large are the number of people who out of fear or stupidity, develop dyspepsia and suffer concomitant poor nutrition and hence loss of weight, strength and efficiency

To treat dyspeptics of this sort the physician must be both dietitian and psychoanalyst to a very considerable degree He must know the elements of nutrition have a simple textbook knowledge of the nutritional values of meats vegetables, and cereals, and though he need not know how to cook he should be able to say what cream soup is and tell how to make beef tea or how long to cook rice when asked And since the day has passed when the doctor merely prescribed phenobarbital and dismissed a neurotic with a knowing silence a pat of reassurance, and a few pills, he must be able to analyze the personality traits of his patient his personal problems, his emotions, if he cannot or will not he is remiss in his duty and denies the patient the very real medicine of his time

Diet in Functional Dyspepsia —What has all this to do with the problem of nutrition? Let us remember that every patient suffering from dyspepsia, of reflex or functional character, or from overeating or undereating requires regulation of his diet Each case requires its own treatment Obviously no simple dietary rule can be set down here

For the large group of patients who suffer from dietary indiscretions, however and that other large group who complain of loss of appetite, epigastric distress fullness after meals belching and constipation certain general dietary regulations are mandatory The normal requirements of at least 100 gm of protein 120 gm or more of fat, and 200 gm of carbohydrate should be met in an appetizing and assimilable form The following diet is suitable for most such patients

Diet for Patients with Nervous Indigestion

Breakfast (8 to 9 A M)

Orange juice or stewed prunes well cooked cereal with milk or cream two pieces of toast and butter one glass of milk or cocoa with milk, or one cup of coffee

Lunch (12 30 P M)

Two eggs any style, baked potato or other well cooked vegetable or noodles and milk (or lettuce salad with hard boiled eggs or asparagus or celery or tomatoes [no mayonnaise]) 2 pieces of toast or old bread milk or cocoa, applesauce stewed rhubarb, baked apple or stewed fruit

Dinner (6 30 P M) (No soup)

Meat or fish boiled or broiled chicken or squab, or 2 small lamb chops broiled, or boiled or roast ham or tongue, steak or roast beef, or plain boiled or broiled seafood such as porgie, flounder, bass, perch, cod, halibut, black fish, whitefish, or oysters, and clams Vegetables baked or boiled potato, spinach (well chopped), purée of green peas or carrots, asparagus, turnips, onions, lettuce, squash boiled white cabbage, or cauliflower Bread 1 slice, toasted Desserts Jello, rice or tapioca pudding, baked apple, rhubarb, stewed or raw berries, stewed fruits, plain cake (such as sponge cake) lady fingers cookies, coffee cake, or ice cream

Such a regimen covers most nutritional needs, it avoids delicatessen foods spiced foods, and condiments, it limits fluids at meals, it regulates the hours of eating and the quality of food at each meal It should remind the patient to eat at regular hours, warn him against haste in eating, and advise him of the necessity for a period of rest and relaxation after each meal for easier digestion

Tobacco, particularly in the form of cigarettes is objectionable in most dyspeptic cases pseudo ulcer syndromes results from the indiscreet use of cigarettes *Alcohol* in general is to be forbidden patients who complain of dyspepsia of any variety, although its role as a relaxant must not be underestimated

Summary —Dietary management of dyspepsia presents many baffling problems to the clinician In reflex dyspepsia treatment of the primary organic disease requires attention The patient with functional dyspepsia requires individual treatment with a generous, nutritionally balanced diet

GASTRITIS

Gastritis is a subject which has come to the fore as the result of the development of the flexible gastroscope, and its acceptance by gastro enterologists In the last century, gastritis was a popular but often erroneous diagnosis In this century, the psychiatrists have emphasized the fact that psychoneuroses often cause gastric complaints, and have popularized in turn the diagnosis of functional disorders of the stomach

Based upon the appearance of the mucosa of the stomach as seen through the gastroscope, gastritis is conventionally divided into an atrophic variety, a hypertrophic form and a mixed variety But in spite of much work certain fundamental facts are lacking The pathologic *substrate* is missing in a large percentage of such descriptions Histologic findings, such as increase in plasma and round cells, proliferation of fibroblasts, and polynuclear cell infiltration are not always consistent with gastroscopic appearance Nor are secretory changes of a chemical nature consistently found in the stomach to accompany hypertrophic gastritis, nor is there any clinical picture which can be consistently related or applied to the diagnosis of gastritis In many such cases of supposed gastritis, one may find a hyperacidity or an anacidity, one may or may not find subjective symptoms of pain, distress, belching, and heartburn Before a true diagnosis of gas-

tritis may be made, there must be a consistent gastroscopic picture, parallel chemical findings, consistent histologic changes in the structure of the mucosa, and a group of clinical symptoms which go hand in-hand with such findings

No clinical area in the gastrointestinal tract remains the center of such varying opinions as does the problem of gastritis While the biopsy table of Wood has helped to clarify the question of the normal and abnormal histology of the stomach in intact man the relation between the histology of the mucosa and syndrome complexes of gastritis (pain anorexia vomiting in relation to meals) remains highly controversial, especially the role of life stress In its treatment the interdiction of tobacco and alcohol seems rational as well as the avoidance of restricted diets It is customary to prescribe a bland type of diet of the ulcer variety and this seems reasonable

Under certain conditions gastritis is a very real manifestation For instance, the gastritis that accompanies a duodenal ulcer usually involves the stomach antrum this has been observed in approximately 40 per cent of all ulcer cases Chronic atrophic gastritis has been said to be a precursor to carcinoma of the stomach Both acute and chronic gastritis with serpiginous ulceration involving the fundus and body of the stomach have been observed too and recognized as a cause of gastric hemorrhage and other gastric disturbances But these are rather rare conditions The well-recognized form of gastritis, localized in the antrum and the pyloric canal which may simulate benign ulcer of the antrum or pyloric canal constitutes a real clinical and pathologic picture This form of antral gastritis was recognized by Konjetzny and other European workers and was carefully observed by Eusterman in a group of cases at the Mayo Clinic Our own experience has led us to add a group of cases, the diagnoses of most of which were confirmed by operation and by gastroscopy

An antral defect is usually noted in the x-ray study a defect which closely resembles ulcer or carcinoma The patient suffers from loss of weight abdominal pain discomfort heartburn loss of appetite and even gross gastric and intestinal hemorrhage The clinical picture is severe and often an alarming one In previous years these patients would have all been operated on for carcinoma It is only at laparotomy that the benignity of the condition was noted Recently the gastroscope has helped avoid the mistake of unnecessary operations To complicate the picture, however, inflammatory gastritis occasionally tends to cause the formation of polyps revealed by x ray, which often bleed and sometimes prolapse through the pyloric canal to cause obstruction and vomiting Without the gastroscope, no clinician would have the courage to deny the possibility of a carcinoma With the gastroscope the polyps may be recognized

Nutrition is seriously affected in some cases of antral gastritis Loss of appetite leads to diminished food intake and food aggravates rather than relieves pain There is a progressive loss of weight and strength too, which often simulates carcinoma to an alarming degree The anacidity that frequently accompanies the atrophic type may interfere with gastric digestion

The problem of gastritis slides imperceptibly into the problem of functional dyspepsia Current trends have emphasized the psychogenic as-

pects of these unfortunate and numerous individuals with upper gastro intestinal symptoms without an organic substrate Caution, however, should be maintained for the time being on the classification of these syndromes "Heartburn," long considered a purely function, neurotic symptom is now recognized as being an esophageal symptom secondary to gastroesophageal reflux Reflux dyspepsia may result from diseases of the biliary tract, pancreas, liver and colon, and their therapy is dependent on the therapy of the primary disorder

Diet —The treatment for this type of gastric disease is a generous nutritive diet and not one of any special type, for the cause of the disease is unknown In cases of varying degrees of hyperacidity or anacidity and the resultant nutritional disturbances, the main attack must be a dietary one, the diet being exceedingly bland and marked by the absence of roughage and condiments All the food should be carefully prepared and pureed, and it should be eaten slowly and never too hot or too cold All textbooks emphasize overeating, bad choice of food, extreme degrees of heat or cold in foods served, and bolting of partially chewed food as causes of gastritis Whether this be true or not, blandness of diet, care in the preparation of food, and *deliberateness of eating are essential points to remember in* treating gastritis The following diet is a representative example of the kind required in the treatment of gastritis

Diet for Patients with Gastritis

Breakfast

Orange juice or stewed prunes, well cooked cereal with milk or cream 2 pieces of toast and butter, ¾ glass milk or thin cocoa and milk

Lunch (12 30 P M)

One boiled egg, baked potato or plain boiled spaghetti (no cheese, but add butter and tomato), or noodles and milk Lettuce and hard boiled eggs (no *mayonnaise) or pot cheese and sour cream may be substituted* Two pieces toast or old bread, vitamin enriched and butter, milk or cocoa Applesauce or stewed rhubarb or baked apple (skinned)

Dinner (7 P M)

Choice of boiled or broiled chicken or squab 2 small lamb chops, broiled, boiled or roast ham or tongue, steak or roast beef, or plain boiled or broiled fish, such as porgie, flounder, bass, perch, cod, halibut, blackfish, whitefish, or oysters and clams Vegetables baked or boiled potato, spinach well chopped, or purée of green peas or carrots, asparagus, turnips, white onions, lettuce squash, *boiled white cabbage, cauliflower* One piece of bread, vitamin enriched Desserts Jello, rice or tapioca pudding baked apple, rhubarb, stewed berries, raw berries, stewed fruits, plain cake such as sponge, lady fingers cookies, coffee cake, or ice cream

PEPTIC ULCER

The patient with *uncomplicated* peptic ulcer as far as is known at present does not suffer from any primary nutritional defect With the develop-

ment of pyloric obstruction and consequent vomiting adequate nutrition cannot be achieved Further, *therapy of peptic ulcer may lead to nutritional imbalance, either because of the inadequate diet of the therapy or* because of surgical distortion of the upper gastrointestinal tract by a variety of anastomotic procedures On the other hand dietotherapy remains of primary importance in the therapy of peptic ulcer itself

Despite the uncertainty which still surrounds the etiology of ulcer, certain features of therapy have achieved an empirical justification (1) The texture of the diet should be soft enough to avoid mechanical trauma to the ulcer (2) the diet should be palatable enough to be acceptable to the patient, but not markedly stimulating to the appetite phase of gastric secretion, (3) the diet should avoid those known protein extractives which stimulate the chemical phase of secretion, (4) the bulk should be so adjusted as to avoid distention stimulus, (5) emphasis should be on the acid neutralizing capacity of the food itself (6) the diet should take maximal advantage of the *acid inhibitory mechanism evoked by the liberation of* enterogastrone by fats and carbohydrates, (7) it should be adequate in those factors known to be involved in wound healing namely, protein and vitamin C (8) known stimulants of gastric secretion, such as alcohol and caffeine-containing beverages should be avoided, (9) specific condiments such as black pepper known to be ulcerogenic in certain experimental and clinical situations should be avoided

Diet in Clinically Active Uncomplicated Ulcer—During the first week, the diet should be most bland consisting of frequent feedings (at two-hour intervals) of food which will neutralize acid The following diet serves as an example of that suggested for the first week

Diet 1

7 00 A M	Milk, ½ cup or 4 ounces (or ¼ cup milk and ¼ cup cream)
7 30	Antacid
9 00	Milk, ½ cup
9 30	Antacid
11 00	Milk, ½ cup
11.30	Antacid
1 00 P M	Milk, ½ cup
1 30	Antacid
3 00	Milk ½ cup
3 30	Antacid
5 00	Milk ½ cup
5 30	Antacid
7 00	Milk, ½ cup
7 30	Antacid
9 00	Milk, ½ cup
9 30	Antacid

It will be noted that it is of prime importance to feed the patient at night, at the last minute before retiring in order to overcome the nocturnal acid gastric secretion which continues throughout the sleeping hours An

pects of these unfortunate and numerous individuals with upper gastrointestinal symptoms without an organic substrate Caution, however, should be maintained for the time being on the classification of these syndromes "Heartburn," long considered a purely function, neurotic symptom is now recognized as being an esophageal symptom secondary to gastroesophageal reflux Reflux dyspepsia may result from diseases of the biliary tract, pancreas, liver and colon, and their therapy is dependent on the therapy of the primary disorder

Diet —The treatment for this type of gastric disease is a generous nutritive diet and not one of any special type, for the cause of the disease is unknown In cases of varying degrees of hyperacidity or anacidity and the resultant nutritional disturbances, the main attack must be a dietary one, the diet being exceedingly bland and marked by the absence of roughage and condiments All the food should be carefully prepared and pureed, and it should be eaten slowly and never too hot or too cold All textbooks emphasize overeating, bad choice of food, extreme degrees of heat or cold in foods served, and bolting of partially chewed food as causes of gastritis Whether this be true or not, blandness of diet, care in the preparation of food, and deliberateness of eating are essential points to remember in treating gastritis The following diet is a representative example of the kind required in the treatment of gastritis

DIET FOR PATIENTS WITH GASTRITIS

Breakfast

Orange juice or stewed prunes well cooked cereal with milk or cream 2 pieces of toast and butter ¾ glass milk or thin cocoa and milk

Lunch (12 30 P M)

One boiled egg baked potato or plain boiled spaghetti (no cheese, but add butter and tomato), or noodles and milk Lettuce and hard boiled eggs (no mayonnaise) or pot cheese and sour cream may be substituted Two pieces toast or old bread, vitamin enriched and butter, milk or cocoa Applesauce or stewed rhubarb or baked apple (skinned)

Dinner (7 P M)

Choice of boiled or broiled chicken or squab, 2 small lamb chops, broiled boiled or roast ham or tongue, steak or roast beef, or plain boiled or broiled fish such as porgie, flounder, bass, perch, cod, halibut, blackfish whitefish, or oysters, and clams Vegetables baked or boiled potato, spinach well chopped, or purée of green peas or carrots, asparagus turnips, white onions lettuce, squash, boiled white cabbage, cauliflower One piece of bread vitamin enriched Desserts Jello, rice or tapioca pudding baked apple, rhubarb, stewed berries, raw berries, stewed fruits, plain cake such as sponge, lady fingers cookies, coffee cake, or ice cream

PEPTIC ULCER

The patient with uncomplicated peptic ulcer as far as is known at present does not suffer from any primary nutritional defect With the develop-

ment of pyloric obstruction and consequent vomiting adequate nutrition cannot be achieved Further, therapy of peptic ulcer may lead to nutritional imbalance, either because of the inadequate diet of the therapy or because of surgical distortion of the upper gastrointestinal tract by a variety of anastomotic procedures On the other hand dietotherapy remains of primary importance in the therapy of peptic ulcer itself

Despite the uncertainty which still surrounds the etiology of ulcer, certain features of therapy have achieved an empirical justification (1) The texture of the diet should be soft enough to avoid mechanical trauma to the ulcer (2) the diet should be palatable enough to be acceptable to the patient, but not markedly stimulating to the appetite phase of gastric secretion, (3) the diet should avoid those known protein extractives which stimulate the chemical phase of secretion, (4) the bulk should be so adjusted as to avoid distention stimulus (5) emphasis should be on the acid neutralizing capacity of the food itself, (6) the diet should take maximal advantage of the acid inhibitory mechanism evoked by the liberation of enterogastrone by fats and carbohydrates, (7) it should be adequate in those factors known to be involved in wound healing, namely, protein and vitamin C, (8) known stimulants of gastric secretion, such as alcohol and caffeine-containing beverages should be avoided, (9) specific condiments, such as black pepper, known to be ulcerogenic in certain experimental and clinical situations should be avoided

Diet in Clinically Active Uncomplicated Ulcer —During the first week the diet should be most bland consisting of frequent feedings (at two-hour intervals) of food which will neutralize acid The following diet serves as an example of that suggested for the first week

Diet 1

7 00 A M	Milk, ½ cup or 4 ounces (or ¼ cup milk and ¼ cup cream)
7 30	Antacid
9 00	Milk, ½ cup
9 30	Antacid
11 00	Milk ½ cup
11.30	Antacid
1 00 P M	Milk, ½ cup
1 30	Antacid
3 00	Milk, ½ cup
3 30	Antacid
5 00	Milk, ½ cup
5 30	Antacid
7 00	Milk, ½ cup
7 30	Antacid
9 00	Milk, ½ cup
9 30	Antacid

It will be noted that it is of prime importance to feed the patient at night, at the last minute before retiring in order to overcome the nocturnal acid gastric secretion which continues throughout the sleeping hours An

alkaline powder or non-absorbable alkali which neutralizes acid should accompany this diet at all stages Liberal amounts of vitamins should be given

If, at the end of one week, the pain is diminished, particularly if the night pain has been completely relieved, the patient may be advanced to the following diet

DIET 2

Breakfast

8 00 A M	Cereal, white cooked, ½ cup
	Milk or milk and cream, 1 cup
	Toast, white dry, 1 slice
	Butter, 1 pat
8 30 A M	Antacid
10 00 A M	Milk, or milk and cream, 1 cup

Lunch or Supper

12 00 NOON	Egg soft boiled, 1, or cottage cheese, 2 oz
	Milk or milk and cream, 1 cup
	Toast, white dry, 2 slices
	Butter, 1 pat
	Fruit, cooked, 1 portion
12 30	Antacid
3 30 P M	Milk or milk and cream, 1 cup

Dinner

5 00 P M	Creamed soup, 4 oz , or cereal, white cooked, ½ cup
	Potato mashed or baked, 1 serving
	Toast
	Milk cooked fruit or junket or custard
5 30 P M	Antacid
8.30 P M	Milk or milk and cream, 1 cup
10.30 P M	Milk or milk and cream or eggnog, 1 cup

This diet should be continued for a week or more, depending upon the rapidity with which pain, particularly night pain, is relieved and the permanence of the relief Night feeding is still to be insisted upon, since otherwise what is gained during the day, when food neutralized acid may be lost during the night, when acid accumulates in quantity and is unopposed by neutralizing factors Alkaline therapy should be continued as before

With the cessation of symptoms, advance should be made to the following diet

DIET 3

Breakfast

8 00 A M	Orange juice (start with small amounts diluted with water) or stewed prunes
	Cereal (well cooked)
	Toast, white 2 slices, crisp with butter
	Milk or cocoa, 1 cup
10 00 A M	Milk 1 cup

Lunch or Supper

1 00 P M	Egg (boiled, poached, shirred or scrambled), 1 or cottage cheese, 2 oz Potato, baked or mashed 1 or noodles (boiled) ½ cup (add milk, no cheese) Jello, or cooked fruit
3 30 P M	Milk 1 cup

Dinner

6.30 P M	Choice of lean beef (boiled broiled or roasted) lamb chop sweetbreads fish or chicken liver Potato, baked or mashed Vegetable puree, 1 serving Toast, white, vitamin enriched, 1 slice with butter Junket custard tapioca pudding rice pudding or baked apple
10 30 P M	Milk or milk and cream mixture

Here, for the first time, meat and fish are added These forms of protein, blandest when well cooked and prepared in the simplest styles, constitute sources of food also capable of neutralizing acid It will be noted that in all three diets limited as they are in classes of food, nutrition can be amply maintained Not only is weight loss prevented, an actual gain of weight is frequently observed under the moderate form of Sippy diet At this point, night feeding may or may not be continued depending on the tendency of night pain to remain absent After the second week on the diet 3, the patient is advanced to diet 4, which is a really liberal and varied menu

DIET 4

Breakfast

8 00 A M	Cereal with milk or cream Toast (white) crisp 2 slices with butter or honey Milk or thin cocoa 1 cup
10 30 A M	Milk, 1 cup

Lunch or Supper

1 00 P M	Choice of eggs 1 or 2, cottage cheese, 2 oz , scalloped dish Choice of baked or mashed potato, macaroni, ½ cup, with butter and tomato noodles, ½ cup with milk Toast, white with butter Choice of stewed fruit, canned fruit ripe banana or pear or junket Milk or cocoa, 1 cup
3 30 P.M	Milk

Dinner

6 00 P M	Broiled steak or roast beef or chicken or lamb chops (2), or lean fish or calves' liver
	Potato, baked or mashed or rice
	Asparagus tips, peas, spinach, beets or carrots
	Toast, 2 slices
	Jello, junket, custard, ice cream, baked apples, stewed fruit, sponge cake or plain cookies
10 30 P M	Milk or eggnog

The Continuous Drip Method —For intractable ulcer, the intragastric *milk drip* is an important subsidiary method of treatment *A patient who fails to react favorably to the Sippy diet, or one of its modifications, will usually be rapidly freed from his pain by administration of a continuous milk drip*

A Levin tube or a thin latex tube is passed through the mouth or the nose into the stomach and connected to a container of milk, the Murphy drip-control regulates the rate of flow Thirty drops a minute of ordinary milk, throughout the day and night gives a total intake of 2,880 cc, or three quarts per twenty-four hours The ulcer is covered with an acid neutralizing food, pain is relieved, clinical symptoms subside, and, above all, nutrition is maintained There is no loss of weight associated with a continuous milk-drip, patients may even gain 1 or 2 pounds in the first days of its administration When the patient is inclined to dislike the tube or to complain of a sore throat from its medial position in the pharynx it is well to compromise During the night, from 8 00 P M, to 8 00 A M the milk-drip is utilized, in the morning, the tube is removed, the patient is placed on his modified Sippy diet, and the administration of Diet 2 is instituted, the last meal being given at 6 00 P M During the next two hours the stomach empties itself At 8 00 P M, the tube is again inserted, the residual content of the stomach is aspirated and withdrawn, the amount being noted and the nocturnal milk drip instituted This method of food by day, milk-drip at night is an ideal method of treatment in the intractable or difficult ulcer case Some clinicians favor the use of *colloidal aluminum phosphate* in one of its available forms as a continuous drip instead of the milk

DIET IN HEMORRHAGE

In cases of hemorrhage early feeding is favored by a great many clinicians ever since the thesis of Meulengracht that ulcer hemorrhage cases are better served by feeding during the hemorrhage than by starvation The older school of clinicians favored large doses of morphia and complete abstinence from all food intake during the hemorrhage They felt that the loss of nutrition during such a fasting period is not great and the overcoming of shock and the controlling of hemorrhage is most important Starvation for a short period associated with continuous intravenous fluids and blood seemed to be the proper therapeutic approach

However Meulengracht has presented good evidence that hemorrhage may be controlled while feeding a patient an abundant diet Further

more, claim is made that nutrition is maintained, loss of weight prevented, convalescence shortened and blood regeneration favored, and under this method the mortality rate is not only *not* greater but actually may be lower than under the older starvation method

For those who favor the Meulengracht regimen, the following menu is appended as a guide

MEULENGRACHT DIET

First Day

6 00 A M	White bread and butter, tea
9 00 A M	Oatmeal with milk, white bread and butter
1 00 P M	Puréed vegetable (peas, carrots) Mashed potato, tea white bread and butter
3 00 P M	Cocoa or tea
6 00 P M	Mashed potato, puréed vegetable, custard, white bread and butter tea

Second Day and Thereafter

6 00 A M	Tea white bread and butter
9 00 A M	Oatmeal with milk white bread and butter
1 00 P M	Cream of vegetable soup (pea potato carrot string bean asparagus) boiled or mashed potato puréed vegetable (peas carrots, asparagus)
	Cooked strained fruit plain rice or tapioca pudding junket Jello plain milk pudding chocolate cornstarch
	White bread and butter tea
3 00 P M	Cocoa or tea
6 00 P M	Cream cheese or eggs (soft boiled or poached)
	Boiled or mashed potato, or cereal with milk and sugar
6 00 P M	Puréed vegetable dessert from above list
	White bread and butter

We will probably all agree that such a diet may be employed in cases of mild hemorrhage where there is little threat to life, certainly we can use such a diet when hemorrhage has ceased and the later stages of recuperation have been reached However, the authors still strongly favor limitation of feeding during active hemorrhage

PYLORIC OBSTRUCTION

Considering that most gastric ulcers of benign nature occur along the lesser curvature of the stomach in the prepyloric region and that most duodenal ulcers are noted within an inch of the pyloric sphincter it is logical to expect in a fair percentage of such cases that the pylorus will become involved in the contiguous inflammatory process and show a resultant narrowing of its lumen In about 26 per cent of gastric ulcer cases and in a smaller percentage of duodenal ulcer cases pyloric obstruction occurs as a complicating factor The ulcer that causes the obstruction may not always be contiguous to or extend into the pyloric canal an ulcer

high up on the lesser curvature may reflexly cause pylorospasm and create the picture of a cicatrizing stenosis But at least half the cases of pyloric stenosis are due to actual edema, an inflammatory reaction about the ulcer, rather than to scar tissue Such obstructive phenomena are clinically transient and can be easily treated by repeated gastric lavage associated with a strict ulcer diet

Many clinicians consider that approximately 80 per cent of cases with vomiting and stenosis are inflammatory in nature and are amenable to conservative therapeutic measures The remaining 20 per cent represent true scar tissue formation at the pylorus or in the pre- or post-pyloric adjoining areas, these scars form a true narrowing of the outlet of the pylorus and materially restrict gastric emptying Among the symptoms of such an obstruction is vomiting, or more truly, vomiting of material which has been in the stomach twelve hours or more

It is not sufficient to ask a patient, "Do you vomit?" Most ulcer patients do vomit "Do you vomit today what you ate yesterday?" "Did you vomit on Tuesday, Monday night's meal?" These questions, if affirmatively answered, indicate a retention of from twelve to twenty four or more hours By *x*-ray examination, retention at six hours of from 25 to 40 per cent of the barium is very significant

On abdominal examination, succussion is evident upon splashing and visible gastric peristalsis may be seen associated with cramping epigastric pain which corresponds to the peristaltic waves crossing over the greater curvature The vomitus is profuse and is expelled once or twice in twenty four hours, usually at night, the vomiting is associated with weakness, loss of weight, evidence of general dehydration, and, eventually, the symptoms of alkalosis and of tetany As large amounts of acid are expelled, alkalosis results, the carbon dioxide combining power of the blood rises from a normal of 50 or 65 volumes per cent to 75 or 85 volumes per cent Nervous irritability, headaches, twitching of the facial muscles, and weakness and prostration occur In the blood, there is a concentration of urea and a fall of plasma chloride sodium and potassium, as well as the rise in the carbon dioxide combining power of the blood plasma

Treatment —The effect of pyloric stenosis on nutrition is marked Food intake is limited due to loss of appetite and continued nausea What food is taken is eventually expelled, in some instances the pylorus is so narrowed that a lead pencil could hardly be passed through the lumen, and retention of gastric content is practically complete The loss of weight is rapid, frequently secondary anemia occurs By means of continuous or frequent lavage, practiced at night, a great deal of the obstruction may be overcome If the stomach is emptied between 8 and 10 P M and the patient left without food overnight, the stomach will regain some of its lost tonicity, in the course of the resting hours it will empty itself of its residual content and allow the patient to begin the day with an empty viscus By continuing this procedure of cleansing the stomach at the end of the day and leaving it at rest all night, amelioration of the symptoms may be obtained in most cases

Each evening the amount of residue in the stomach should be measured and, if possible, titrated for acid The progressive diminution in the

amount of residual gastric material suggests clinical amelioration Here the prognosis is good and the conservative method of treatment will probably relieve the stenosis and allow the patient an indefinite period of good health

If however, the evening residue does not diminish, or retention persists as soon as the lavage is discontinued medical treatment is no longer indicated a surgical approach is necessary

In order to obviate the loss of weight during this period of lavage and cleansing, it is necessary to administer the meals in the form of highly concentrated and nutritious foods The fats, such as butter and cream, are not well tolerated in the presence of obstruction, a diet must be chosen on a simple protein carbohydrate basis Milk, all of the well cooked cereals and meat products should form the basis of such a diet Cereals should be strained and eaten with sugar and milk eggs should be taken soft-boiled or in eggnog bread should be crustless and scant in quantity Junket, Jello, and cream soups should be given The following menu is a fair one for the early phase of a case of pyloric stenosis

Menus for Patients with Pyloric Stenosis

First and Second Day

To 1 quart of milk add ½ pint of cream shake well and keep on ice Of this mixture drink ½ glass every two hours One half hour after drinking this milk, take 1 powder (as prescribed in a wineglass of water)

Third to Seventh Day Inclusive

8 00 A M	¾ glass of milk a portion of well cooked cereal (cook farina for one half hour, oatmeal for two hours, rice for four hours), 1 piece of toast and butter
10.30 A M	¾ glass of milk 2 zwieback or 2 Holland rusks or graham crackers
1 00 P M	1 egg medium or hard boiled a glass of milk 2 pieces of toast and butter a portion of apple sauce
3 30 P M	Glass of milk 2 zwieback or rusks
7 00 P M	Cream soup (cream of celery soup cream of spinach, etc) baked potato with butter, 1 piece of bread and butter a baked apple of which the pulp only is eaten, or 4 well cooked prunes with the skin removed

Note Wherever milk is indicated, the mixture of cream and milk is preferable One half hour after each of these main meals a powder should be taken in a little water As the condition improves meats in the form of chopped hamburger or lamb chops ham, or plain boiled fish may be added

In all cases where there has been loss of fluids, they should be replaced intravenously as a continuous drip normal saline with 5 per cent glucose and added potassium at the rate of 30 drops per minute

Diet in Connection with Surgery for Obstruction —If nutrition is materially upset and obstruction is obviously complete, it is necessary to resort to surgery In the more advanced cases, a gastro-enterostomy and vagotomy can be performed, under spinal anesthesia this is a satisfactory pro-

cedure Under the special threatening circumstances of alkalosis and mal nutrition, however, the possibility of a gastrojejunal ulcer is a likely one, and may unfortunately follow rapidly upon the creation of a new stoma But such dire possibilities must be discounted and the preferable operation of subtotal gastrectomy frequently denied the patient because of the increased surgical risk, and vagotomy added to enterostomy

In extreme cases, cases in which nutrition has been badly interfered with, chemical imbalance is present or threatening, and water and electro lyte balance is completely disturbed, the safest and the wisest procedure is to perform a preliminary jejunostomy Such an operation, under local or spinal anesthesia, is a simple performance The stomach is now put com pletely at rest, no food being allowed, the patient is fed every two hours, by means of a catheter entering the jejunostomy, from 4 to 8 ounces of a variety of formulas The formula of one of these is as follows

Scott-Ivy Pabulum Jejunostomy Feeding

Milk	6 cups
Cream	2 cups
Cane sugar	12 tablespoons
Flour	1 cup
Water, warm	2000 cc
Salt	2 tablespoons

When mixture is cooked, add

Peptone	1 cup
Egg	½
Vitamin C	75 mg
Drisdol	4 drops
Brewers yeast	2 tablespoons

60 calories in 1 ounce I S P

This formula or preferably the Hollander-Rosenak aliment, marketed as "Pregestal'®, may be made up in bulk and fed slowly by means of gravity into the jejunostomy opening, if this is done, nutrition increases, gain in weight begins to take place, and chemical equilibrium begins to approach normal Such maintenance of nutrition by means of jejunostomy feeding may be continued for from four to six weeks, until the gain of weight and the general clinical improvement is marked At this point it is preferable to perform a subtotal gastrectomy, maintaining the jejunostomy for post operative feeding purposes, particularly to obviate post operative gastric atony, such as frequently follows an enlarged surgical procedure After a few days, small feedings by mouth are begun, the jejunostomy is allowed to close eventually, as the patient progresses rather slowly through Diets 2 3 4, and 5, as previously indicated under treatment of ulcer

Summary —Diet is less important than lavage in overcoming gastric retention Feeding should be administered sparingly during the day, the last meal should be at six o'clock the stomach should be emptied about 10 P M Some cases of pyloric obstruction are really instances of inflammatory

pyloric spasm and can be successfully handled by lavage and restricted diet

DIET FOLLOWING SURGICAL THERAPY FOR PEPTIC ULCER

Although the surgery of choice for peptic ulcer is constantly undergoing revision and re-evaluation, it is fair to summarize contemporary thinking as follows For uncomplicated peptic ulcer not responding to medical therapy the operation of choice is a subtotal gastrectomy of at least 75 per cent of the stomach, with a complimentary infra-diaphragmatic vagotomy A close second choice is that of gastro-enterostomy and vagotomy In either event the question arises whether the patient with these operations should remain on an ulcer diet post-operatively In the light of present-day operative results there would seem to be little rationale for a rigid restriction of the patients food intake Discretion suggests that a rather bland diet be followed for at least the first few months post-operatively with a gradual return to a regular complete diet

DIET IN THE UNFAVORABLE CONSEQUENCES OF SURGERY

1 **The Post-gastrectomy Dumping Syndrome** —In a small but definite percentage of patients following subtotal gastrectomy an unpleasant and occasionally quite distressing set of symptoms supervene to which the label post-gastrectomy "dumping syndrome' has been affixed Weakness, palpitation sweating tremulousness, faintness and occasionally upper abdominal discomfort may occur At present these symptoms are ascribed to precipitous emptying of the gastric remnant These symptoms occur at times promptly after meals and may re-occur one to one and a half hours later These late symptoms have been ascribed to hypoglycemia and possibly hypopotassemia It should be added that the mechanism of these complaints is far from being completely understood The basic principles of dietotherapy in this syndrome are to delay, if possible, the rapid gastric emptying and secondly, to prevent wide variations in blood sugar by substituting protein and fat for easily assimilated glucose The diet in these patients should be a rather dry one with restricted fluids high in protein and fat and low in simple monosaccharides But it should be added that the dietary treatment of the severe "dumping syndrome" is unsatisfactory in some individuals

2 **Nutritional Failure Following Subtotal Gastrectomy** —A small group of patients develop as their only distressing sequelæ of operation the inability to regain lost weight or slight gradual continued loss of weight Examination of the majority of these patients reveals no recurrence of ulcer, the small bowel *x*-ray pattern and transit time are within normal limits, and the stools do not have excessively large amounts of fat or nitrogen Diminished appetite is a prominent complaint as well as inability to eat the former sized meals The management of these patients is trying both to the physician and the patient Substitution of 6 small

rather than 3 usual size meals is often necessary. Diet should be a high caloric one, high in protein *with moderate fat and sugar*. But here again, as in the "dumping syndrome," dietary management of these individuals is relatively unsatisfactory. Vitamin supplements are conventionally employed, and with the role of vitamin B_1 and intrinsic factor in absorption still not completely clarified, it seems justifiable to give them on an empirical basis. The use of emulsifiers to improve fat absorption in this condition has been advocated but the evidence which has been presented is not convincing.

THE MANAGEMENT OF THE OBESE PATIENT WITH ULCER DISEASE

A word should be devoted to the question of the overweight ulcer patient. As a result of the conventional ulcer treatment, many patients gain weight. In addition, the peptic ulcer patient who is grossly overweight presents a serious risk when definitive surgical therapy is contemplated for his ulcer or its complications. In addition, experienced observers have all noted exacerbation or recurrence of ulcer symptoms in individuals subjected to marked caloric restriction or rapid weight reduction regimens.

In order to prevent further weight gain in the already overweight ulcer patient, the basic ulcer diets (3 through 5) should be modified by substituting fat-free skim milk for all milk, and milk and cream servings. Bread, *potatoes, spaghetti, and macaroni should be eliminated*. The use of frequent feedings of protein in the form of meat, gelatin or Jello, fish, pot cheese and cottage cheese will serve to control gastric acidity and ulcer pain and limit the caloric intake.

In the grossly overweight patient whose weight is being reduced prior to ulcer surgery, slow reduction is desirable. He should receive conventional antacid therapy, even though the ulcer is not active, in the form of non-absorbable alkalies and the newer cholinergic blocking agents.

HIATUS HERNIA

For the purpose of systematizing the dietary treatment of hiatus hernia it is possible to divide them into two main groups: (1) Paraesophageal hernia with pressure symptoms and (2) sliding hiatal hernia with esophageal reflux and heartburn. In addition both types may develop ulceration: (1) within the hernia, (2) marginal ulceration in the esophagus and both may bleed.

While *surgical therapy* should be considered in all haitus hernias the majority of patients can be managed, and usually are managed, by medical measures alone.

In general, the *therapeutic regimen* aimed for is one which avoids raising intragastric pressure markedly, avoids the reclining position after meals, promotes prompt gastric emptying and diminishes reflux of acid gastric juice into the esophagus by *antacid measures*. Thus, the diet is similar to the basic ulcer regimen. The liberal ulcer diet (Diet 4 above) is a satisfactory starting point. The diet should be divided into approximately 5

small meals, the last of which should be eaten five to six hours before retiring for the night

In addition, the diet should be somewhat drier than the standard ulcer diet the large amounts of milk or skimmed milk should be considerably reduced Fluids between meals, especially carbonated beverages whether calorically significant or not should be omitted

Ulceration in a hernia or associated with a hernia should be vigorously treated with the series of diets outlined before in the section on peptic ulcer The development of bleeding in association with hiatus hernia should be treated as outlined in the section on Hemorrhage in Peptic Ulcer

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Chapter 22 (*Continued*)

B Nutrition in Disease of the Intestinal Tract

By J ARNOLD BARGEN

WHEN one considers the importance of the various segments of the digestive tract in nutrition and bodily economy, the intestine must be placed at or near the top of the list The intestine is such an important part of the digestive tract not only because it plays a major part in the digestion of food but, and much more important, because it is almost totally responsible for the absorption of nutrient material The importance of digestion in the stomach and the part that the liver and pancreas play in human metabolism cannot be underrated but if the important products which these organs prepare could not be absorbed they would be of no use to the human body Any disturbance of the intestine, small or large reflects heavily on the human economy Tremendous loss of weight and unbelievable general debility may result from a variety of intestinal disorders

In discussing nutrition from the standpoint of the intestinal tract, it is well to divide the disorders which might disrupt human nutrition into five major groups The dietary problems will then be discussed from the standpoint of the manner in which each of these affects the bodily nutrition

IRRITABLE BOWEL SYNDROME

The commonest intestinal disorder, which frequently seriously upsets human nutrition, has been discussed under a variety of designations, of which "irritable bowel syndrome" is probably the most descriptive Such terms as the "unstable colon," "dyssynergic colon," "mucous colitis," "spastic colitis," "fermentative colitis," and many others have been introduced from time to time by various writers on the subject to describe this syndrome, but none of them seem to quite include all the manifestations associated with this condition nor is the term "irritable colon" entirely descriptive However, it immediately suggests that the intestinal disorder under consideration is only part of a general disorder It is a name applied to a functional disorder of the digestive tract in which intestinal symptoms are paramount In this condition, the patient may be constipated to a marked degree or have periodic loose stools and sometimes severe diarrhea [1]

Our present-day life, with its hustle and bustle, its tremendous competition in wage earning and its every urge for speed, often interferes with proper care of intestinal function There results, therefore, a "nervous indigestion" in which the colon plays no small part After a morning rush to the office there often follows an all-day rush in a highly competitive business A person does not have time to stop for evacuation of the bowel The executive who sits in an office all day likewise does not have time for

adequate evacuation of the bowel In both cases there is improper intake of fluids The noonday meal is eaten hurriedly and under the most adverse conditions At night, such a person probably eats his dinner hurriedly to prepare for the evening's activities He retires late only to arise again improperly rested and to go through the same procedure as on the previous day

The farmer's activities are of a different type but he too must rush, and even the common laborer is at times beset with the "hurries" of life which are too much for him But no one is more troubled than the lady of society, whose life consists of one round of competitive entertaining and of irregular eating and drinking For such women then, come a variety of abdominal discomforts and to them as Munthe in his *Story of San Michele* has pointed out, the term "colitis" has only too commonly been used as a placebo to soothe their anxious minds

Every great social upheaval is followed by much so-called nervous indigestion and disruption of normal intestinal function This may be merely a functional disturbance, which, however, may result in great suffering and discomfort On the other hand, it may be a real intestinal disease

Among the local irritants, cathartics and colonic irrigations are often used to the point of creating great discomfort and much overactivity, not only of the colonic mucous membrane but of the wall of the bowel as well Frequently intestinal disturbances follow ingestion of some foods Rarely more than a few foods affect a single person Sea foods, berries, whole wheat or bran, heavy pastry chocolate nuts and fried foods are common offenders The adherence to dietary fads of the type adopted by women to make their figures conform to current fashion frequently has resulted in the appearance of symptoms of irritable colon

Although rarer than sensitiveness to certain foods, sensitiveness to the bacteria normally present in the intestinal canal has been demonstrated A lack of hydrochloric acid in the gastric contents has been found to stimulate intestinal overactivity

Basically the sensitive colon may be inherited, for it is common to see members of several generations of one family suffer similarly Once a woman shows marked signs of the disturbance she is likely to suffer with it at intervals for the rest of her days The more fortunate members of affected families suffer from the typical symptoms only rarely as when they are going through some severe emotional strain

Neurogenic trends almost invariably are present Nervous tension anxiety worry the presence of crowds, introspection, insomnia unhappiness, family difficulties and dissipation in one form or another have been given to me as causes which precipitated the abdominal disorders It is clearly understood then, why occupation has a definite bearing on the condition and why teachers, clergymen lawyers, salesmen merchants, students and draftsmen are affected so much more frequently than farmers and laborers The symptoms usually make their appearance early in life but they may be precipitated by any nervous strain at any time of life

Wakefield and Mayo[3] have pointed out the effect that social maladjustment of some persons has on the production of an irritable colon They illustrated this well by their graphic arrangements of the factors playing a

part in the causation of the irritable colon, comparing the development of the condition to a wheel, the hub of which represents a social crisis affected by its spokes, the various modifying factors

It can be said, then, that overwork, overeating, insufficient rest, nervous fatigue, nervous tension, exposure, local irritation caused by laxatives and colonic irrigations, foods, and the bacteria that normally are present in the intestine rank prominently among the causes of this colonic dysfunction

Obviously then, no single dietary program will be satisfactory for all forms of this condition Frequently these patients have untold abdominal misery and discomfort, much more severe than would come from the more serious conditions to be discussed later

Under these conditions a very bland type of diet, including frequent small feedings, may be indicated The diet will vary with the symptom of constipation or of diarrhea Even with the former, a bland protective diet should form the basis of this part of the treatment The plan behind any diet for relief of constipation is to supply enough material which will not be absorbed in the small intestine but will go into the colon and add bulk

Some persons do not tolerate much bulk in foods Such persons should include in their diet fruit juices, eggs, bacon, mushes without bran puffed cereals, white bread, toast, butter, milk, cream, soups, beef, lamb, fish, chicken, oysters, sweetbreads, liver, potato, rice, sweet potato, asparagus tips, beets, creamed spinach, young carrots, cooked celery, turnips, purées of beans, sweet corn passed through a colander, tender string beans, peeled tomatoes, cooked pears and peaches, bananas, cottage cheese, simple puddings, custards, ice cream, gelatin, plain cake, stewed fruit, baked apples and stewed prunes To this diet may be added one of the less irritating bulk producers such as cellothyl (methyl-cellulose), 3 or 4 tablets with each meal, or granulated agar The latter may be taken in doses of 1 or 2 tablespoonfuls (15 to 30 cc) a day, in soup, milk, cereal, fruit juices or jelly Other satisfactory bulk producers include preparations of karaya gum and other harmless and nonabsorbable gums Mineral oil may be taken in minimal quantities

Persons who can eat almost everything with comfort should include in their usual diet prunes, figs, dates, raisins, peaches, pears, apples, apricots, pineapple, plums, cherries, berries, melons, bananas, oranges, grapefruit, spinach, asparagus, celery, tomatoes, cauliflower, eggplant, cabbage, sprouts, string beans, turnips, squash, carrots and the like Salads are helpful, whole-wheat bread has value

All should drink quantities of water and their intake of fluid should be equivalent to 10 to 15 glasses (2 4 to 3 6 liters) daily Water at room temperature is advisable and it may be wise to add a pinch of salt to each glass

Sample meals for a day are given in Table 58

Meals should be regular to make the bowels move regularly No meal should be omitted People should eat slowly, chewing the food well, for these are necessary stimulants to the colon to push the residues along

A relation between irritable colon and food allergy has been suggested by some physicians, others have seen parallelism between irritable colon and bronchial asthma, hay fever, urticaria and angioneurotic edema In those instances in which possible sensitivity to protein or other food exists,

elimination diets might be tried It is hardly necessary to place all instances of intolerance to individual foods on the basis of allergy Often the offending foods act by direct irritation to the bowel

TABLE 58 —SAMPLE MEALS FOR PATIENTS WITH IRRITABLE BOWEL SYNDROME

Breakfast	*Dinner*	*Supper*
Prunes six	Potato with butter or gravy	Vegetable soup
Breakfast food	Carrots	Cauliflower
Cream or top milk and sugar	Roast beef	Beet and egg salad with mayonnaise
Graham bread and butter	Head lettuce with mayonnaise	Graham bread
Bacon	Graham bread with butter	Baked apple
Postum tea or coffee	Fruit gelatin	Milk
	Milk	

Skin tests so often helpful in discovering the causes of hay fever, are seldom of value in revealing the foods that the patient should not eat Elimination diets are time-consuming and in the average case a simpler method can be employed The patient is instructed to make a written record of all foods consumed in the twenty-four hours before each attack of unexplained abdominal pain, passage of increased amounts of mucus in the stool or diffuse abdominal discomfort By this method it may be found that some one article of diet was taken before each attack, or it may be observed that an unusually large amount of some commonly used food was eaten The elimination diet is but a variation of this method and various physicians have used different basic diets Alvarez[4] has suggested a basic diet of lamb, rice, butter, sugar, lemon gelatin and canned pears If on this narrow diet symptoms do not occur the problem is almost solved, because from there on an additional food at a time may be added, testing it for three or four days Every added substance put into the mouth must be viewed with suspicion Chewing gum, candy, paraffin oil or agar must not be used during the period of observation

Among the commoner offending foods are milk, eggs, pork, wheat products, honey, sea foods, cabbage, cheese, chocolate and berries but there are many others If symptoms of nausea, gas and biliousness occur after any addition, the added food should be eliminated temporarily Other foods should be tried in orderly fashion Frequently small quantities of foods may be taken when large amounts would make trouble

When symptoms of indigestion continue during the time in which the patient adheres to the narrow diet the problem becomes more difficult Too often, however the symptoms are not attributable to any particular foods and the physician soon discovers a fussy, unreliable, neurasthenic and complaining person who may have traveled many miles to find relief but who is unwilling to follow simple dietary suggestions

Most patients who have an irritable bowel and loose stools do well on the diet outlined for the average patient suffering from chronic ulcerative colitis It may be necessary to omit certain foods but in the main this diet serves very well

In some cases it is well to begin management with a diet of very low residue, allowing the colon the greatest possible rest A sample diet of such foods might very well include the items shown in Table 59

TABLE 59 —LOW RESIDUE DIET FOR PATIENTS WITH IRRITABLE BOWEL SYNDROME

Breakfast	*Dinner*	*Supper*
Fruit juice 1 glass	Broth, clear	Broth
Heavy cream	Gelatin or custard	Steamed rice
Egg	Heavy cream	Heavy cream
Butter	Fruit juice	Fruit juice
Cookies or crackers of low residue	Arrowroot cookies	Cookies
Coffee	Tea	Tea or coffee

TABLE 60 —LOW RESIDUE DIET

Approximate Food Value Protein, 60 gm Calories 2 000

Diet outline		*Sample menu*
Breakfast		*Breakfast*
Cereal bland	1 serving	Puffed Wheat
Cream	½ cup	Cream
Bacon	2–3 strips	Bacon
Egg	1	Coddled egg
Toast	1 slice	Toast
Butter	1 square	Butter
Coffee if desired		Coffee
Dinner		*Dinner*
Meat soup (no vegetable)	1 serving	Chicken soup with noodles
Meat or fish	1 serving	Broiled steak
Potato	1 serving	Potato in half shell
Gravy, if desired		
Bread white or rye	1 slice	Bread
Butter	2 squares	Butter
Dessert, bland (no fruit)	1 serving	Creamed tapioca
Cream	2 tablespoonfuls	
Tea if desired		Tea
Supper		*Supper*
Meat or fish	1 serving	Roast chicken
or		
Eggs	2	
Rice steamed	1 serving	Steamed rice
Bread white or rye	1 slice	Bread
Butter	2 squares	Butter
Dessert, bland (no fruit)	1 serving	Jelly
Cream	2 tablespoonfuls	Cottage pudding
Tea if desired		Tea

To such a diet may be added candy in variable amounts Other additions may be made as improvement warrants, including lean meat, cheese, toast, banana, bread, boiled milk potato, shredded lettuce and concentrated vitamins, in the order named

Alcoholic beverages are often poorly borne by the person who has an irritable colon My experience would suggest that if there is the slightest question of their being tolerated, they should be avoided

The foods and sample menus shown in Table 60 would serve well for a person with a markedly irritable bowel syndrome associated with frequent or loose stools

TABLE 61 —STANDARD ANTICONSTIPATION DIET

Approximate Food Value Protein, 70 gm Calories, 2 000

Diet outline		*Sample menu*
Breakfast		*Breakfast*
Fresh fruit	1 serving	Prunes
Whole-grain cereal	1 serving	Oatmeal
Bacon	2 strips	Bacon
or		
Egg	1	
Whole-wheat bread	1 slice	Whole-wheat bread
Butter	1 square	Butter
Cream	½ cup	Cream
Beverage as desired		Coffee
Dinner		*Dinner*
Cream soup	1 serving	Vegetable soup
or		
Milk	1 glass	
Meat, fish or fowl	1 serving	Swiss steak
Potato	1 serving	Mashed potatoes
Vegetable	1 serving	Harvard beets
Salad fruit or vegetable	1 serving	Molded fruit salad
Whole-wheat bread	1 slice	Whole-wheat bread
Butter	1 square	Butter
Cream	2 tablespoonfuls	Cream
Dessert	1 serving	Baked apple
Beverage, as desired		Milk Coffee or tea
Supper		*Supper*
Meat fish or fowl	1 serving	Cold meat
or		
Eggs	2	
Potato rice or macaroni	1 serving	Spanish rice
Salad fruit or vegetable	1 serving	Buttered carrots Cabbage salad
Whole wheat bread	1 slice	Whole-wheat bread
Butter	1 square	Butter
Fruit	1 serving	Apricot tapioca pudding
Milk	1 glass	Milk
Beverage, as desired		Cream
3 P M and 8 P M fruit juice	1 glass	Coffee or tea

Note If necessary more vegetables and fruits as well as more fruit juice may be added to the foregoing diet [8]

On the other hand for a person who is badly constipated and has the irritable bowel syndrome, the dietary regimen shown in Table 61 would be very helpful This diet contains 600 gm (6 servings) of fruit and vegetables

other than potato with 2 glasses of fruit juice, whole-wheat bread and whole-grain breakfast cereals Six to 10 glasses of water should be taken during the day

DEFICIENCY STATES INCLUDING THE SPRUE SYNDROME

There are a variety of conditions in which damage to the small intestine has occurred to a point where there is great interference with intestinal absorption of foods, liquids, and other metabolites essential for proper nutrition and sometimes life itself Among these may be included certain disturbances of the pancreas, for example, stones in the duct of Wirsung, ileojejunal insufficiency such as that occurring in late stages of regional enteritis, diseases involving the mesenteric lymph nodes, and short-circuiting procedures, which sometimes are necessary, as in cases of extensive mesenteric thrombosis and pellagra, but the major deficiency syndrome is undoubtedly best represented by the sprue syndrome

In the past the sprue syndrome has presented great difficulties in dietary management This does not mean that all the difficulties have been resolved, however, since the discovery that gluten is an important factor in the production of this condition, or at least in its development, the feeding problem has become easier in many of these patients

In the malabsorption syndrome known as sprue, there is marked atrophy of the mucosa and tissue of the bowel wall Considerable data have been accumulated which suggest that there is selective absorption in different portions of the small intestine and, since the atrophy of any given human intestine is not uniform it follows that objective tests rarely reveal disturbances of absorption or signs of deficiency that are similar in any two given cases The poor absorption of fat is, of course, a common observation but the degree of this, too is variable Nowhere in the digestive tract is there so much disturbance of nutrition as for lesions of the small intestine It is the major source of absorption and assimilation An intact intestinal wall, a normally functioning mucous membrane normal peristalsis, normal transportation of chyme, the presence of adequate digestive enzymes and bile, and intact lymphatics are all essential to adequate digestion and absorption

If any of these are disturbed or the small intestine is affected in different portions in the manner observed in sprue, a deficiency state will eventuate In some individuals there will be a disturbance of absorption of glucose as evidenced by the so-called flat glucose tolerance curve In other individuals there will be an increase in prothrombin time suggesting failure of absorption of vitamin K and associated with hemorrhagic tendencies In some individuals there will be a disturbance of calcium absorption illustrated by tetany In others there will be failure of iron absorption resulting in a microcytic hypochromic type of anemia In other individuals there will be a decrease or lack of folic acid resulting in a macrocytic anemia sometimes difficult to differentiate from [illegible] anemia In all there will be a variable increase [illegible] the amount of [illegible] and possibly also fat secretion so that [illegible] the stools a[illegible] of more than fifty per

cent of fat This condition varies greatly in individuals and again serves to illustrate that the objective evidence of failure to absorb is directly related both to the amount and distribution of small bowel damage So, in these conditions of small bowel disturbances, the factor of absorption is the most important one to be kept in mind when preparing the diet Experience of recent years has shown that a gluten free diet is much better borne by these individuals and many individuals who eat such a diet become asymptomatic Just how much change in the structure of the intestine will develop by this change in diet remains to be shown The dietary program used at the present in the care of patients with certain types of sprue is illustrated in Tables 62, 63, 64 and 65

TABLE 62 —GLUTEN FREE DIET—APPROXIMATE COMPOSITION

	Amount
Protein	115 gm
Fat	115 gm
Carbohydrate	275 gm
Calories	2570
Calcium	970 mg
Iron	16 mg
Vitamin A	3800 I U
Thiamine	1 0 mg
Riboflavin	2 1 mg
Niacin	15 mg
Ascorbic Acid	150 mg

Adequacy and General Description —This diet fails to meet the recommended dietary allowances of the National Research Council for thiamine

This diet has no gluten Wheat rye and oats and products containing wheat rye and oats are omitted In general, the diet is high in protein and calories has a moderate amount of fat and the amount of residue is restricted

Each patient with sprue should receive multiple vitamin capsules as well as adequate calcium lactate and in addition at least four mg of water soluble vitamin K twice a week or oftener Further vitamin supplements may be needed in the individual case In acute exacerbations of the disease it may be necessary to increase the amount of sodium chloride In general the diet is low in fat and high in protein carbohydrate and calories The amount of residue is restricted A large proportion of the carbohydrates used are those from fruits and simple sugars (fructose and glucose) The actual amount of food allowed will depend upon the activity of the condition For needed calories increases in fats and starches may be allowed Such a program will vary with the extent of bowel damage and consequent severity of symptoms While the dietary program of sprue probably serves the most important purpose of diet in any digestive disorders other measures of therapy are also of importance The use of extra amounts of calcium vitamin K, and at times even the use of steroids will serve to improve the absorptive power of such a damaged small intestine The diet will be increased as the absorptive power of the intestine is increased The problem then becomes one of maintenance of this absorptive power and this has not always been found possible

TABLE 63 —FOODS INCLUDED AND EXCLUDED IN GLUTEN FREE DIET

Type of food	*Foods included*	*Foods excluded*
Beverage	Carbonated beverages cocoa, coffee, whole milk (no more than 2½ cups daily) tea	Cereal beverage chocolate flavored beverages malted milks drinks made with malt
Bread	Bread and muffins made without wheat, rye, or oat flour	Bread made with wheat, rye or oat flour, crackers
Cereal	Corn kix, cornmeal, puffed rice	Any cereal made with wheat oats or rye, any cereal with malt flavoring
Dessert	Blancmange, custards, gelatin desserts, sherbet, tapioca pudding all without nuts and without fruits except those in ' Foods Included Those high in fat to be used only occasionally Special cookies made without wheat or rye or oat flour	Any containing wheat rye or oat products as cakes, cookies, commercial ice cream pastries pie, commercial puddings
Fat	Butter, fortified margarine, mayonnaise, French dressing 2 squares (14 gm or 1 tablespoon) daily More if fat is well tolerated	Cream, salad dressing
Fruit	Any fruit or juice except those listed under Foods Excluded'	Fruits with tough skins or seeds Raw apples, cantaloupe honeydew melon, watermelon if indicated
Meat, egg or cheese	Any meat, fish or fowl except those listed under Foods Excluded" at least 8 ounces (240 gm) daily cottage cheese eggs, at least 2 daily	Fried meat, fish fowl or eggs bacon luncheon meats sausage cheese other than cottage cheese
Potato or substitute	Potatoes, white refined rice	Fried potato potato chips sweet potatoes, hominy, macaroni noodles, spaghetti
Soup	Fat-free broth or bouillon vegetable soup and milk soup made from Foods Included '	Cream soups and soups containing wheat or wheat products
Sweets	Glucose honey jelly corn syrup sugar as tolerated, hard sugar candy	Candy containing fruit nuts, chocolate wheat or wheat products candy high in fat content jam, marmalade
Vegetable	Any except those listed under Foods Excluded' Corn and lima beans should be puréed	Vegetables with tough skins, fibers or seeds Dried beans, broccoli, Brussel sprouts, cabbage cauliflower, cucumbers, kohlrabi, onions, dried peas, green pepper radishes, rutabagas sauerkraut, turnips if indicated
Miscellaneous	Salt spices in small amounts, vinegar	Alcohol chocolate, gravy herbs malt extract nuts olives pickles popcorn, white sauce

TABLE 64.—DIETARY PATTERN AND SAMPLE MENU FOR GLUTEN FREE DIET

Dietary pattern			
Breakfast		*Wt gm*	*Approximate measure*
Fruit juice	Orange juice	100	½ cup scant
Fruit	Grapefruit	100	½ medium
Cereal	Cornmeal	15 (dry)	½ cup (cooked)
Eggs	Soft cooked eggs	100	2
Bread	Barley muffin	50	1
Butter	Butter	5	½ square
Beverage	Coffee		1 cup
Whole milk	Whole milk	120	½ cup
Sugar	Sugar	15	1 tablespoon
Jelly or honey	Jelly	20	1 rounded teaspoon
Dinner			
Meat	Roast beef	120	4 ounces
Potato	Boiled potato	100	½ cup
Vegetable	Sliced beets	75	½ cup
Salad	Shredded lettuce	30	3 small leaves
Dessert	Sherbet	70	⅓ cup
Whole milk	Whole milk	240	½ pint
Bread	Soybean muffin	50	1
Butter	Butter	5	½ square
Jelly or honey	Jelly	20	1 rounded teaspoon
Supper			
Meat	Cold roast beef	120	4 ounces
Potato	Baked potato	100	1 medium
Vegetable	Green string beans	75	½ cup
Salad	Canned pear salad	75	½ pear
Dessert	Sliced banana	100	1 medium
Whole milk	Whole milk	240	½ pint
Bread	Soybean muffin	50	1
Butter	Butter	5	½ square
Jelly or honey	Jelly	20	1 rounded teaspoon

The latter feature is the one which can usually be varied according to the nature of the ulcerative process

For instance, in the streptococcal form of ulcerative colitis (thrombo-ulcerative), the disease begins in the rectum, resulting in a bottle-neck type of narrowing of the distal segments of the large intestine (Fig 57, *a*) In

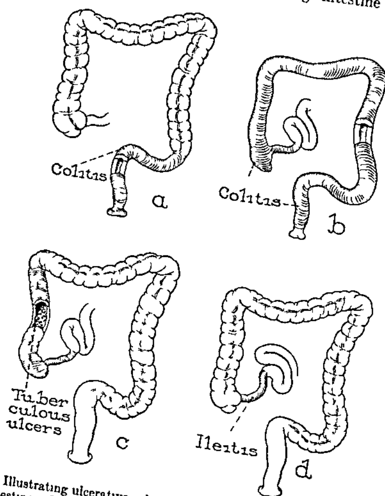


Fig 57 —*a* Illustrating ulcerative colitis with lesions limited to the distal segments of the large intestine *b* Illustrating the narrowed tubelike large intestine of advanced and extensive ulcerative colitis (thrombo ulcerative type) *c* Illustrating the ulcerative process and site of involvement in intestinal tuberculosis *d* Illustrating the changes in the small intestine in a typical case of regional enteritis

contrast to this the lesions of tuberculosis (Fig 57, *c*) involve the ileocecal coil and ascending colon thus producing a tuberculous ulcerative colitis The lesions of amebic colitis primarily involve the right half of the large intestine The lesions of the form of ulcerative colitis following as a rather late phase of bacillary dysentery may affect any portion of the intestine Then too, there is a form of ulcerative enteritis involving primarily the distal segments of the small intestine (Fig 57, *d*), that is, the distal ileum and associated with this condition there is frequently marked infiltration of the wall of the bowel, with thickening of the wall and narrowing of the lumen

in the diet are that it shall not be irritating that it shall be of low residue, that it shall have an adequate content of calories, proteins vitamins and minerals and that it shall be offered as attractively as possible Some of the foods of low residue are lean meats, rice, white bread, Italian pastes, sugar, well-cooked and strained cereals, cooked eggs, butter and cream

TABLE 66 —DIETARY REGIMEN FOR PATIENTS WHO HAVE CHRONIC ULCERATIVE COLITIS[6]—FOUNDATION DIET*

Breakfast	*Dinner*	*Supper*
Cereal† bland 1 serving	Meat soup without vegetables 1 serving	Steamed rice 1 serving
Cream ½ cup	Meat 6 ounces	Meat or fish 4 ounces
Bacon 4 strips	Potato 1 medium sized	Bread white or rye 1 slice
Egg 1	Gravy, if desired	
Toast 1 slice	Bread white or rye, 1 slice	Butter 2 squares
Butter 2 squares	Butter 2 squares	Bland dessert‡ without fruit 1 serving
Coffee if desired	Bland dessert‡ without fruit 1 serving	Cream 2 tablespoonfuls
Sugar	Cream 2 tablespoonfuls	Tea if desired
Vitamin B complex	Tea if desired	Sugar
	Sugar	Vitamin B complex
	Vitamin B complex	

* Order of additions to foundation diet
One banana very ripe
Orange juice ½ glass
Vegetable purée 2 tablespoonfuls
Milk in the form of cream soup or milk toast
Whole milk 2 glasses
Bland fruit canned or cooked peaches apricots pears white cherries strained applesauce baked apple without skin, 1 serving
Cream 2 glasses added to milk so that each glass contains half milk and half cream
Tomato juice ½ glass
Whole cooked vegetable 2 servings (purée omitted) including as desired young tender carrots beets cauliflower buds squash string beans asparagus and green lettuce cut very fine with plain mayonnaise or cooked dressing if desired

† Cream of Wheat Farina Puffed Rice Puffed Wheat Corn Flakes Rice Krispies or strained oatmeal

‡ Custards cornstarch puddings junkets gelatin desserts without nuts or fruit plain rice tapioca or bread puddings simple cakes and cookies and plain ice cream

Proteins in most forms are very desirable Vitamins can be supplied in concentrated form in fruit juices, yeast, butter wheat germ, cod liver oil extract or irradiated ergosterol Contrary to the usual assumption, milk is not a low-residue food, and it is not well tolerated by many patients Boiling the milk makes it slightly more digestible It is very often necessary to start the treatment of these patients in the hospital, where their activities can be controlled accurately even though they may not be acutely ill On this basis a very definite dietary program has been outlined On admission the patient is given strictly bland food to which additions are made at

TABLE 68 —LIST OF FOODS INCLUDED IN, AND EXCLUDED FROM DIETARY PROGRAM FOR CHRONIC ULCERATIVE COLITIS—FOUNDATION DIET*

Type of food	*Foods included*	*Foods excluded*
Beverage	Carbonated beverage (not iced), cereal beverage decaffeinated coffee and coffee in most cases	Milk
Bread	White enriched or fine rye bread white crackers toast	Whole-wheat graham dark rye bread
Cereal	Refined cereals corn rice wheat, dry cereals prepared from them, cooked oatmeal	Whole-grain cereals
Dessert	Plain cakes, cookies, custards gelatin desserts ice cream, pie puddings rennet desserts, all without fruit or nuts	Desserts containing fruits or nuts
Fat	Butter cream margarine	Any other
Fruit	None	All
Meat egg or cheese	Bacon tender meat fish fowl, canned fish, eggs cheese	Tough meat
Potato or substitute	Potato macaroni, noodles, refined rice spaghetti	Hominy unrefined rice
Soup	Bouillon broth	Cream soup vegetable soup
Sweets	Plain candy honey, jelly sugar, syrup	Candy containing fruit or nuts, jam
Vegetable	None	All
Miscellaneous	Cream sauce gravy peanut butter spices in moderation vinegar	Nuts olives, pickles popcorn, relishes

* Additions to the foundation diet to make full diet

Addition 1 —Ripe banana ½ or orange juice ½ glass

Addition 2 —Tomato juice ½ glass or vegetable purée 2 tablespoonfuls with dinner and supper

Addition 3 —Boiled milk 1 glass, cream soup or milk toast

Addition 4 —Pasteurized milk (not boiled) 2 glasses dry skim milk powder or nonfat milk solids milk, half cream as tolerated meat servings increased to 4 ounces with each meal

Addition 5 —Bland fruits that is avocado canned or cooked apple apricots cherries peaches pears, purée of stewed fruit (except prunes in some cases) all without seeds or skins a third glass of milk

Addition 6 —Whole cooked vegetables 2 servings that is canned or cooked asparagus beets carrots green beans peas pumpkin squash purée of corn or lima beans shredded lettuce salad dressing

who treats the patient and the dietitian is never better illustrated than in the management of the various forms of ulcerative colitis When the lesions primarily involve the proximal segments of the large intestine or the distal segments of the small intestine a quite different situation prevails (Fig 57, *c* and *d*) This is the case in regional enteritis and tuberculosis, and there is usually an associated diarrhea, hence every effort should be made to keep the foods as nonirritating, as low in residue, and as bland as pos sible Also since there is a good deal of interference with intestinal ab sorption, extra quantities of such vitamins as C, B and K should be allowed

TABLE 69 —DIETARY PATTERN AND SAMPLE MENU FOR CHRONIC ULCERATIVE COIITIS—FOUNDATION AND FULL DIETS

		Foundation diet		*Full diet*	
Dietary pattern	*Sample menu*	*Weight gm*	*Approximate measure*	*Weight gm*	*Approximate measure*
		BREAKFAST			
Fruit juice*	Orange juice			100	½ cup
Dry skim milk*	Dry skim milk			15	2 tablespoonfuls
Cereal*	Farina	15 (dry)	½ cup (cooked)	15 (dry)	⅓ cup (cooked)
Bacon	Bacon	15	1–2 strips	15	1–2 strips
Egg	Soft cooked eggs	100	2	100	2
White bread	Toast	40	2 slices	40	2 slices
Butter	Butter	14	2 squares	14	2 squares
Beverage*	Tea		1 cup		1 cup
Cream	Cream 20 per cent	75	⅓ cup	75	⅓ cup
Sugar	Sugar	7	½ tablespoon ful	7	½ tablespoon ful
Jelly	Jelly	20	1 rounded tea spoonful	20	1 rounded tea spoonful
		DINNER			
Soup*	Broth	100	½ cup	100	½ cup
Meat*	Roast beef	120	4 ounces	120	4 ounces
	Gravy	50	¼ cup	50	¼ cup
Potato	Mashed po- tato	100	½ cup	100	½ cup
Vegetable*	Buttered beets			75	⅓ cup
Salad*	Egg salad			50	1 egg
Salad dress ing*	Mayonnaise			15	1 tablespoon ful
Dessert*	Vanilla ice cream	70	⅓ cup	70	⅓ cup
Milk ½ cream	Milk ½ cream			240	½ pint
Dry skim milk	Dry skim milk			30	4 tablespoon fuls
Beverage*	Tea		1 cup		1 cup
Bread*	White bread	40	2 slices	40	2 slices
Butter	Butter	14	2 squares	14	2 squares
Sugar	Sugar	7	½ tablespoonful		

			SUPPER		
Meat or substitute*	Cold sliced ham	60	2 ounces	120	4 ounces
Potato or substitute*	Baked potato and butter	100	1 medium	100	1 medium
Vegetable*	Buttered green beans			75	⅓ cup
Salad*	Canned pear salad			75	1 half
Salad dressing*	Fruit salad dressing			15	1 tablespoonful
Fruit* or dessert*	Sliced banana			100	1 medium
	Chocolate pudding	100	½ cup		
Milk, ½ cream	Milk, ½ cream			240	½ pint
Dry skim milk	Dry skim milk			30	4 tablespoonfuls
Beverage*	Tea		1 cup		1 cup
Bread*	White bread	40	2 slices	40	2 slices
Butter	Butter	14	2 squares	14	2 squares
Sugar	Sugar	7	½ tablespoonful		

* Note limitations listed in Table 68

By and large, the diet in these patients varies with the extent and severity of the disease and with the systemic changes which the disease has wrought in the bodily economy

INTESTINAL PARASITES

A variety of intestinal parasites have their habitat in the digestive tract of man Among those commonly encountered may be mentioned Endamoeba histolytica, hookworm, Schistosoma nematodes, flukes tapeworm Giardia lamblia and many others Most of them cause only an intestinal irritation, resulting in frequent bowel motions which may be watery or simply occur as frequent formed stools, the result of an intestinal irritation Of course, the important therapeutic endeavor in these cases is to free the host from these parasites Often however, even after the parasite has been dissipated, there remains an irritable intestine and so the dietary program discussed under the irritable bowel syndrome is often indicated in patients who have or who have had intestinal parasites

The major exception to this generalization is Endamoeba histolytica The presence of this parasite in the human intestine may be associated with extensive ulcerative disease, and under these conditions a carefully planned dietary program such as has been described for the various phases of ulcerative colitis may be advisable This diet should be varied according to the severity and activity of the amebic infection Many patients with amebic infection do not require any dietary restrictions In many others it becomes advisable to offer some restrictions even after the amebæ have been eradicated because of the irritable bowel syndrome produced

This discussion in a symposium on nutrition in health and disease is advisable only because fairly frequently as a result of the physician's orders or of the patient s own volition the patient s diet has been restricted

much too much because of infestations by intestinal parasites It is important that a very reasonable attitude toward this subject be constantly borne in mind and it is well to remember that only a few of these intestinal parasites cause actual intestinal ulceration and that the important therapeutic problem is to eradicate the parasite and not nurture it

INTESTINAL NEOPLASMS

The large intestine has among other functions the function of storage of the food residue Therefore, in patients with intestinal neoplasms who

TABLE 70 —DIETARY PROGRAM FOR USE BEFORE AND AFTER OPERATIONS ON THE LOWER PART OF THE INTESTINAL TRACT
Minimum Residue (M R) Diet—Approximate Composition*

	Unit	*Half diet*	*Full diet*
Protein	gm	35	75
Fat	gm	55	105
Carbohydrate	gm	115	245
Calories		1,100	2 230
Calcium	mg	410	610
Iron	mg	6	11
Vitamin A	I U	3,600	4,300
Thiamine	mg	0 5	1 2
Riboflavin	mg	1 0	1 6
Niacin	mg	3	10
Ascorbic acid	mg	60	70

* A variation of 10 to 15 per cent in the composition of the diet is assumed

TABLE 71 —FOODS INCLUDED IN AND EXCLUDED FROM MINIMUM RESIDUE DIET

Type of food	*Foods included*	*Foods excluded*
Beverage	Carbonated beverage, cereal beverage, coffee, tea	Milk, milk drinks
Bread	Refined bread or toast, crackers, rusks	Whole-grain bread hot bread
Cereal	Cooked refined cereals cornmeal strained oatmeal refined rice, commercial products prepared from them	Whole-grain cereals other prepared cereals
Dessert	Plain cakes, plain cookies custards gelatin desserts water ice or ice cream without fruit or nuts plain puddings, rennet desserts	Pastries
Fat	Butter or substitute, cream	None
Fruit	Strained fruit juice	Any other
Meat egg or cheese	Bacon ground or tender beef, chicken, fish, ham lamb liver or veal eggs cottage or cream cheese, Cheddar (American) used as flavoring	Fried meats tough meats pork other cheese
Potato or substitute	Macaroni noodles refined rice spaghetti	Potato hominy, whole-grain rice
Soup	Bouillon broth	Cream soup, thick soups
Sweets	Hard candy milk chocolate, plain creams, gumdrops, jelly marshmallows, sugar, syrup	Other candy, jam marmalade
Vegetable	Tomato juice	Any other
Miscellaneous	Cream sauce, gravy, salt, spices, vinegar	Nuts, olives, popcorn

TABLE 72.—DIETARY PATTERN AND SAMPLE MENU FOR MINIMUM RESIDUE DIET

Dietary pattern	*Sample menu*	*Half diet*		*Full diet*	
		Weight gm	*Approximate measure*	*Weight gm*	*Approximate measure*
BREAKFAST					
Fruit juice	Orange juice	100	½ glass	100	½ glass
Refined cereal	Farina	7 (dry)	¼ cup (cooked)	15 (dry)	½ cup (cooked)
Eggs	Soft cooked eggs	50	1	100	2
White toast	White toast	10	½ slice	20	1 slice
Butter	Butter	7	1 square	7	1 square
Beverage*	Coffee		1 cup		1 cup
Cream	Cream	50	¼ cup	75	⅓ cup
Sugar	Sugar	7	½ tablespoonful	7	½ tablespoonful
Jelly	Jelly			20	1 teaspoonful
DINNER					
Broth	Broth			100	½ cup
Meat*	Roast beef	30	1 ounce	90	3 ounces
	Gravy	25	⅛ cup	50	¼ cup
Potato substitute	Buttered noodles	50	¼ cup	100	½ cup
Dessert*	Vanilla ice cream	70	⅓ cup	70	⅓ cup
White toast	White toast	10	½ slice	20	1 slice
Butter	Butter	7	1 square	7	1 square
Jelly	Jelly			20	1 teaspoonful
Beverage	Tea		1 cup		1 cup
Sugar	Sugar	7	½ tablespoonful	7	½ tablespoonful
SUPPER					
Meat or substitute*	Cold sliced ham			60	2 ounces
Potato substitute	Steamed rice	7 (dry)	¼ cup (cooked)	15 (dry)	½ cup (cooked)
Dessert	Chocolate pudding	50	¼ cup	100	½ cup
Cream	Cream	30	2 tablespoonfuls	50	¼ cup
White toast	White toast	10	½ slice	20	1 slice
Butter	Butter	7	1 square	7	1 square
Jelly	Jelly			20	1 teaspoonful
Beverage	Tea		1 cup		1 cup
Sugar	Sugar	7	½ tablespoonful	7	½ tablespoonful
BETWEEN MEAL FEEDINGS					
10:00 A.M.	Fruit juice with sugar	100	½ glass	200	1 glass
3:00 P.M.	Baked custard or gelatin dessert	50	¼ cup	100	½ cup

* Note limitations listed in Table 71

are to undergo operation, it is important that as little residue as possible be accumulated in the intestine above the neoplasm prior to any operation, and so we have gradually developed a dietary program (Tables 70, 71 and 72) for these patients which has served in a very satisfactory manner, giving a suitable complement of calories and a minimal amount of residue

Adequacy and General Description —The half minimum residue diet is below the recommended allowances of the National Research Council in almost every respect It is for temporary use only The full minimum residue diet is below the recommended allowances in calcium, iron, vitamin A, niacin and ascorbic acid One to three vitamin supplements may be ordered by the physician for patients who are using the diet

The half minimum residue diet is routinely ordered for a few days post operatively The use of concentrated sweets is temporarily limited

The full diet is served to patients before operation and is resumed a few days after operation on the lower part of the intestinal tract It is adequate in protein and calories and has a minimum of residue Milk is omitted except as it is used in cooking, and no cream soups are allowed If a high calorie diet is desired, it should be ordered as a 3,000 calorie minimum residue diet Calories are added to the full minimum residue diet (2,230 calories) chiefly in the form of fruit juice, sugar and candy

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Chapter 22 (*Continued*)

C Nutritional Aspects of Liver Disease in Man

By ROBERT M KARK

DIET therapy is the accepted handmaiden of bed rest in the modern management of patients ill with diseases of the liver On the other hand, the part played by ill-balanced diets and secondary nutritional disorders in the pathogenesis of hepatic diseases in man is presently the center of controversy

Everyone seems to agree that malnutrition can, and does, produce functional, structural, and clinical alterations of the liver in Kwashiorkor and other types of "fatty" liver But, many deny that nutritional hepatic injury is the cause of Laennec's cirrhosis Minot and his colleagues demonstrated that dietary deficiency was a factor in the production of alcoholic neuritis, and Patek in 1941, observed that a good diet, rich in B-complex vitamins, was of great benefit to alcoholic patients ill with cirrhosis of the liver[26]

Following these observations, a wide variety of acute and chronic disturbances of the liver were produced in animals by experimental manipulations of diets These studies supplied the theoretical basis for present clinical concepts

NUTRITIONAL FACTORS IN EXPERIMENTAL LIVER DISEASE IN ANIMALS

A series of experimental studies on the dietary production of hepatic disease which continues at present has been recently reviewed by Popper and Shaffner[31]

The two significant lesions produced in the experimental animal are fatty liver and massive hepatic necrosis These often occur together and were first separated in 1944, by Himsworth and Glynn[24] Nutritional fatty liver is the result of a deficiency of the so called lipotropic substances which may act as methyl donors During subsistence on abnormal diets, mild fatty changes have been observed to progress, in the experimental animal, to the formation of large fatty cysts within groups of liver cells Later, connective tissue septa form and are followed by collapse of the liver lobules fibrosis, and hepatic cellular regeneration Eventually, hepatic carcinoma may develop

Diets deficient in cysteine vitamin E and a third factor presumably selenium produce massive hepatic necrosis in rats The animals may die or if they survive, post-necrotic scarring or cirrhosis of the liver may develop

All these lesions have their prototypes in hepatic disease common to man and the natural history of cirrhosis in alcoholics or following severe

infective hepatitis seems to bear a close resemblance to what has been seen in the experimental animal.

A note of caution is proper at this time to those eager to transfer concepts based on dietary hepatic disease in rats to the interpretation of hepatic disease in man. Elias has shown that the microscopic structure of the liver of the rat is different from that in man. Other studies seem to indicate that the rat's portal circulation is different functionally from man's. In addition, the nutritional requirements of the rat, especially for methionine, vary considerably from man's needs.[85]

Nutritional Aspects of Liver Disease in Man.—(a) *Introduction.*—In man, hepatic injury may be the result of consuming an improperly balanced diet (Kwashiorkor), the result of consuming toxic substances with the diet (senecio cirrhosis), the result of consumption of an excess of a nutrient in the face of a metabolic disorder (iron intake in hemochromatosis), the result of a caloric excess (fatty infiltration of the liver), and the result of a conditioned deficiency which may interfere secondarily with hepatic and general nutrition (*e.g.*, the fatty liver seen in patients with ulcerative colitis). Be this as it may, there is no doubt that once the liver is severely damaged, the general nutritional welfare of the body suffers, and the majority of patients with chronic liver disease come to the physician nutritionally bankrupt. Their nutritional disturbances range from pellagra to starvation and from hemorrhagic hypoprothrombinemia to massive protein depletion. Every known nutritional syndrome has been described in association with hepatic disorders, and to add insult to injury, vigorous therapy has, in recent years, precipitated sodium, potassium, and magnesium deficiency states in the edematous or ascitic patient with liver disease.

A simple classification of liver diseases in man is shown in Table 73. These conditions will be discussed from the nutritional point of view, and in addition broad topics—such as hepatic coma, re-feeding gynecomastia, hypoprothrombinemia, and ascites—will be reviewed.

TABLE 73.—CLASSIFICATION OF LIVER DISEASES WITH SPECIAL EMPHASIS ON THOSE OF NUTRITIONAL ORIGIN

1. The fatty liver and Laennec's or "portal" cirrhosis
   - Post-viral
   - Dietetic* { primary / conditioned / "toxic" }
   - Alcoholic*
   - Banti's syndrome
   - Unknown
2. Hepatolenticular degeneration*
3. The Fanconi syndrome*
4. Hemachromatosis and hemasiderosis*
5. "Toxic" cirrhosis*
6. Biliary cirrhosis (xanthomatous biliary cirrhosis)
7. Cardiac cirrhosis
8. Endocrine cirrhosis (methyl testosterone jaundice)
9. Infective or parasitic cirrhosis

* Indicates conditions primarily of nutritional origin

EXPERIMENTAL NUTRITIONAL HEPATIC DISORDERS IN MAN

As far as is known, the only report of the experimental production of nutritional hepatic dysfunction in man was the study carried out at Elgin by Horwitt, Rothwell, and Kark[12] on diets inadequate in protein

In the summer of 1950, patients from The Elgin State Hospital were chosen as subjects for a study of niacin and tryptophan requirements They lived on the experimental diets (Table 74) for the next two years

TABLE 74 —BASAL DAILY NUTRIENT INTAKE OF SUBJECTS STUDIED AT ELGIN

2300 calories
40 gm protein (Zein = 7 gm Gelatin = 3 5 gm)
93 gm fat
5 8 mg nicotinic acid
265 mg tryptophan
0 4 mg riboflavin

Caloric balance of subjects was maintained at levels of 90 to 120 per cent of the basal diet as determined during a two-month preliminary study period

None came down with pellagra However enlarged livers and abnormal tests of liver function developed in several subjects, while rats, fed the same diets, developed fatty livers The abnormalities in both species were prevented or repaired by supplementing the experimental diets with protein (lactalbumin or milk and meat diet)

The observations in this experiment are pertinent to present speculations and to future research on Kwashiorkor and alcoholism with cirrhosis,[1] which occurs in populations eating low protein, high caloric diets

NUTRITIONAL ASPECTS OF INFECTIOUS HEPATITIS

The various forms of infectious hepatitis which disturb mankind include those produced by viruses (*e g* yellow fever), bacteria (*e g* brucellosis), spirochetes (*e g* syphilis), fungi (*e g*, histoplasmosis), protozoa (*e g*, amebiasis), and helminths (*e g* schistosomiasis)

Unfortunately, the nutritional aspects of most infectious diseases involving the liver have not been studied, save for the two viral infections—virus A (infectious hepatitis) and virus B (serum hepatitis) These two diseases have been studied very thoroughly because of their high incidence in military populations Two broad questions need consideration with regard to virus A and virus B infectious hepatitis

1 Are malnourished non immune individuals more liable to infection with these viruses than well-nourished individuals?

2 Does diet therapy affect the course of these diseases?

In Western civilizations infective hepatitis, a relatively benign condition, is the most common single hepatic disease seen in clinical practice It hits the young, the healthy and the well nourished

Few critical studies have been done on rates of infection in malnourished populations infected with hepatitis. After World War II there were no reports of overwhelming epidemics in prisoner-of-war camps. During the war, the attack rate of infectious hepatitis in well-nourished, meat-eating Indian soldiers was no different from that observed in ill nourished, vegetarian Indian soldiers (Jats) who eschewed meat on religious grounds.

Capps was the first to indicate that convalescence was prolonged in soldiers ill with virus A infectious hepatitis (catarrhal jaundice) if food intake was inadequate, especially if it was inadequate in protein. He presented data to show that soldiers whose diet was inadequate during their illness were more prone to death, complications, and prolonged convalescence. In addition, it was observed that the consumption of alcoholic beverages during or soon after recovery from infectious hepatitis was often followed by a relapse or prolonged convalescence. Capps' observations have led to the general belief that patients with infectious hepatitis should be fed a low fat, high protein, high caloric diet while they are ill. This is extremely difficult to do, since low fat diets are extremely unpalatable. Fortunately, more recent investigations have shown that moderate fat diets are not contraindicated in the treatment of infectious hepatitis.

The most thorough studies of dietary requirements in infectious hepatitis have been carried out recently by the United States Army on soldiers ill with infectious hepatitis who were studied in a military hospital in Japan.

These studies indicate that optimal dietary intakes shorten convalescence. The food actually consumed each day during the illness provided, under optimal conditions, approximately 40 calories/kg of body weight, protein consumption was at approximately 13 per cent of total calories, fat consumption was at approximately 30 to 35 per cent of calories, and the remainder of the calories were provided from carbohydrate sources. A very slight increase in the efficiency of the metabolic mixture was noted when the protein content of the diet was increased to 19 per cent of total calories.

The partition of nutrients described above is very similar to those consumed each day by healthy, active soldiers, studied by Johnson and Kark during World War II. On the average, these healthy soldiers consumed, in temperate climates, 3600 calories per day. Thirteen per cent of the calories were provided by protein, 40 per cent came from fat, and the remainder from carbohydrate sources.

DIETARY MANAGEMENT OF UNCOMPLICATED INFECTIOUS HEPATITIS

General Conditions.—The United States Army experience indicates that the best results are obtained when the full dietary regimen is instituted as soon as the diagnosis is made.

It is true that anorexia is a cardinal symptom of infectious hepatitis, but even severely anorexic patients will improve rapidly if they force themselves to eat. To this end, the physician should explain to the patient, in some

detail, the reasons for the type of diet therapy which is employed He must indicate the dangers of starvation and an unbalanced diet and should persuade, suggest, and educate the patient The patient must be aware that the dietary prescription provides "medicine" not just "food" This emphasis on food consumption should be stressed to the patient by the dietitian by the nursing staff, and by others—such as family or visitors—who have contact with the patient Occasionally the threat of stomach tube feedings will be needed to convince recalcitrant patients of the need to eat

A well balanced nutritious, mixed diet contains all of the essential nutrients needed by patients ill with acute hepatitis This should be provided by attractive meals served at *regular* intervals (*e g*, 7 30 A M, 12 30 P M, and 6 00 P M) when the patient is most likely to be hungry, and by interval feedings of milk shakes or eggnogs (10 00 A M, 3 30 P M, and 10 00 P M)

Hot food must be served hot and cold food cold! Servings of overdone steam moistened meat covered with lukewarm gravy, and lumpy mashed potatoes which float in cooking water from overboiled vegetables, are enough to turn the stomach of a ravenous adolescent, let alone a bilious patient! Unfortunately this sort of meal is all too often served on the standard diet for patients in hospitals The diet for the patient with infectious hepatitis should be a "special diet" ordered for an individual Therefore the diet prescription should be discussed with the dietitian, with special emphasis on the proper spacing of foods and in between meal feedings, together with techniques for the stimulation of appetite As it is important to know exactly what the patient has consumed each day the dietician or the nursing staff should weigh or measure (household measures) and record on the hospital chart plate-wastage after each meal or small in between meal feeding Food should not be brought to the patient by relatives or visitors

If the above measures do not insure an adequate intake of food, then food should be given by tube feedings (see page 655) Intravenous feedings of glucose and amino acids will rarely be needed if the patient is urged to eat

Calories —The patient should actually consume (not merely be served) 40 to 45 calories per kg body weight per day This would be about 3000 calories per day for a 70 kg man These required intakes can also be calculated on the basis of approximately 20 calories per pound per day

The patient's meal should be planned to provide the required calories and *all* food presented to the patient should be consumed He must be impressed with the absolute necessity of clearing his tray It is not wise to overload the meal trays with excess food and excess calories above requirements, as this may be rather discouraging If a patient feels hungry on his planned diet, he should be given larger in between meal feedings or his meals should be increased The more ill the patient, the more important it is to insure an adequate intake of calories, and it is usually he who must be urged or forced to eat

Protein —The protein intake of the patient with infectious hepatitis will be satisfactory if he consumes between $1\frac{1}{2}$ to 2 gm of protein per kg body weight per day This is easily obtained from a well planned mixed diet

which will give between 105 and 140 gm of protein for a man weighing 70 kg (154 lbs) The protein should come from both animal and vegetable sources Adequate supplies of choline, inositol, methionine, and other amino-acids are provided in mixed Western protein containing foods, such as meat, fish, milk, cheese, eggs, bread, and potatoes Therefore, special amino-acid supplements are not necessary It is also not necessary to give protein hydrolysates, as protein digestion is not disturbed in uncomplicated infectious hepatitis

During the first few days of the illness when appetite is poor, patients will often enjoy and consume individually prepared broiled (not pan fried) hamburgers They will eat these when they will not eat roasted or stewed meat As a matter of fact, we insure adequate protein intake in the initial phases of the illness by serving broiled hamburger (cooked to the patient's taste) for breakfast as well as lunch and dinner These seem to be more acceptable early in the illness than lean, lamb chops or steaks, which may be added to the diet as appetite recovers

Recently it has been shown that high protein intakes are contraindicated in hepatic coma[28] (see below) and until the situation is clarified, it would be prudent to keep oral protein intakes within the limits set above and to reduce it to very low levels in critically ill patients

Fat —There is no need to restrict fat intake in patients ill with infectious hepatitis Fat is beneficial when supplied at a "normal" level High fat diets are not necessary and may be harmful, but at 30 to 35 per cent of calories per day, they add palatability to the diet Patients ill with infectious hepatitis are not usually intolerant to fatty foods In general, it is wiser to provide fat through dairy products (eggs, milk, butter, ice cream, cheese) than through fatty meats or pies or fried foods, such as fried onions

Carbohydrate —An adequate carbohydrate intake is readily obtained, provided that a well-balanced diet is consumed in accordance with the principles noted above It is the custom in many hospitals to provide hard candy *ad libitum* to patients ill with infectious hepatitis This should not be done as continuous sucking at sweets disturbs the appetite and provides an unbalanced source of calories

Vitamins —A liberal diet prepared from fresh foods in accordance with standards laid down in Chapter 21 provides all the vitamins and minerals required by the patient ill with infectious hepatitis Care must be taken to insure dietary sources of ascorbic acid (citrus fruits, tomato juice) as well as sources of B complex vitamins No harm will follow prescription of the daily requirements of nutrients in the form of a vitamin capsule but large doses of synthetic vitamins are unnecessary Although vitamin B_{12} has been advocated by some as a specific measure for the treatment of infective hepatitis, the data from the United States Army investigation do not support its special use—nor are particular benefits to be expected from vitamins A, D, or E

In infectious hepatitis the plasma prothrombin level is often reduced This is usually the result of disturbed liver function The damaged liver is unable to synthesize prothrombin, and it is therefore unable to use

vitamin K. However, intrahepatic biliary obstruction does occur in infective hepatitis, and occasionally the exclusion of bile from the gut will interfere with absorption of vitamin K. Under these conditions, parenteral vitamin K or oral, water soluble vitamin K will effectively raise prothrombin levels. In 1940, Kark and Souter showed that under these conditions the degree of response of prothrombin levels to vitamin K therapy was a good index of hepatic function.

Large amounts of vitamin K are not necessary, a 5 mg tablet of menadione sodium bisulfite U S P, once a day, is usually sufficient.

Water and Electrolytes.—Usually, gross sodium and water retention does not complicate infectious hepatitis. Although it is true that recovery from infectious hepatitis is often ushered in with a diuresis it is only in the severely ill patient that sodium retention by the kidney needs to be treated through strict dietary regulation of salt and sodium containing foods. When this is necessary, the low salt regimen, prescribed for the treatment of cirrhosis of the liver, should be followed. In uncomplicated infectious hepatitis, salty foods (such as bacon) should be eschewed, and the salt shaker should not be left on the patient's tray. Beyond these simple precautions, no other restriction of sodium is necessary.

IN-BETWEEN-MEAL FEEDINGS

For supplementary feeding of calories and protein, the milk shakes described below may be used.

TABLE 75.—FORMULAS FOR MILK SHAKES

Standard Skim Milk Powder Milk Shakes
(41 gm protein 31 gm fat, 70 gm carbohydrate 735 calories)

Ingredients	*Grams*	*Ounces*	*Approximate Measure*
Milk	250	8⅓	1 cup
Eggs	100	3⅓	2
Skim milk powder	40	1⅓	7 tbsps level
Sugar	20	⅔	1⅓ tablespoons
Ice cream	80	2⅔	1 inch slice
Cocoa*	5	⅙	2 tbsps level
Vanilla	f d		Flavor desired

Standard Casec Milk Shake
(44 gm protein 30 gm fat 50 gm carbohydrate 600 calories)

Ingredients	*Grams*	*Ounces*	*Approximate Measure*
Milk	250	8	1 cup
Eggs	100	3⅓	2
Casec	20	⅔	5 tbsps level
Sugar	20	⅔	1⅓ tablespoons
Ice cream	80	2⅔	1 inch slice
Cocoa*	5	⅙	2 tbsps level
Vanilla	f d		Flavor desired

* Note that other types of flavoring should be used so that the chocolate milk shake does not become too monotonous.

Recently a number of powdered supplementary foods (easily reconstituted by adding water or milk) have been marketed. One of these (Sustagen) is excellent in many respects. It is a bland, "balanced" food fortified with vitamins at a therapeutic level, and its cost per gram of protein is not excessive.

The palatability of all these drinks depends to a very great extent on the thoroughness of mixing of the preparation. Electric milk shake mixers are ideal, but Dover beaters, etc., are satisfactory if used with care and thoroughness. The milk shakes should be made up fresh each day and kept refrigerated from preparation until service.

When low sodium supplementary or in between-meal feedings are necessary, the following may be used.

TABLE 76.—LOW SODIUM SUPPLEMENTARY FEEDING
(Lonalac 50 gm., protinal * 35 gm., glucose 20 gm., water, 200 cc.)

	Composition
Calories	465 (approx.)
Protein	35.0 gm. (approx.)
Fat	14.0 gm. (approx.)
Carbohydrate	49.5 gm. (approx.)
Sodium	21.0 mg.

* Casec may be used to replace protinal but it is not quite as pleasant unless the drink is flavored with a sodium free syrup.

Small servings of these milk shakes should be given between breakfast and lunch and between lunch and supper. A large serving should be given the last thing at night before retiring.

Alcohol.—Consumption of alcoholic beverages should not be allowed during the illness and for six months after recovery. This should be discussed with the patient.

COMPLICATIONS

When the patient with infectious hepatitis comes under medical care, the damage within the liver is done and diet therapy only serves to hasten healing and regeneration of the hepatic cells. Thus diet therapy cannot stem the overwhelming hepatic insufficiency which kills one patient in a thousand. There are grave doubts in my mind that optimal diet therapy prevents the relentless march to cirrhosis which develops in some patients with hepatitis (1 per cent), nor does it seem able to prevent laboratory and clinical relapses seen in approximately 5 per cent of those admitted to hospitals with hepatitis. In infancy and childhood, fortunately infectious hepatitis nearly always runs a benign course, but in pregnancy it is often virulent.

When infectious hepatitis or serum hepatitis develops in the third trimester of pregnancy the prognosis for mother and child is usually grave, while in the first trimester no ill effects usually ensue provided that treat-

ment is vigorous. Hepatitis which appears during the second trimester of pregnancy is a more serious complication than hepatitis which develops earlier. It is not known whether endocrinologic, metabolic, or nutritional factors are responsible for the malignant nature of hepatitis in the terminal stages of pregnancy.

The complications of infectious hepatitis require modifications of dietary management. The most common complications are nausea and vomiting, which may have to be managed with tube feedings or intravenous feedings. The other complication is progression toward severe hepatic insufficiency, which requires separate consideration, as indicated under the section Hepatic Coma Syndrome. The dietary management of chronic hepatitis is no different from that of cirrhosis of the liver and is discussed on page 666 under this heading.

Tube or Gavage Feeding.—When anorexia, nausea or vomiting are severe enough to limit caloric intake, tube feeding should be instituted without delay. One of the most significant advances in therapeutics in the past years has been the recognition that thin polyethylene or nylon tubing can be used for gavage feeding of individual patients for weeks at a time, without causing distress to the patient and without damage to the mucous membranes of the upper respiratory or gastro intestinal tract. When once passed it can usually be left in place. The patient can eat his usual meals without discomfort during the day with the tube in position and during the night while he sleeps, a gavage feeding such as Sustagen can be run into his stomach or duodenum. Gavage or tube feeding sets are now available commercially.

In pre-coma or in comatose patients, the danger of aspiration pneumonia as a result of regurgitation of stomach contents must be kept in mind. Allergic reactions to the plastic tubes have also been reported. Recently a number of motor-driven pumps have been used to insure a constant delivery of feeding mixtures to the patient and we feel that this is a useful adjunct to gavage feeding.

Intravenous Feeding.—The indications for intravenous feeding are stupor, coma and vomiting. Intravenous feeding may also be used as a supplement to oral or gavage feeding especially to supply salt-free amino acid supplements to low protein diets. It is difficult at present to provide a completely satisfactory intravenous diet. Calories are difficult to provide, as commercially produced intravenous fat solutions are not available as yet. With regard to carbohydrate, fructose (10 per cent) and invert sugar (10 per cent) (a natural mixture of dextrose and fructose) solutions are now available as alternatives to glucose. Fructose is a useful source of carbohydrate which apparently does not require insulin for its immediate metabolism. For long term intravenous feeding these carbohydrates should be run into veins through fine plastic catheters which reduce the dangers of a reactive phlebitis. A useful technique for giving adequate intravenous calories is to pass a catheter down the jugular vein into the superior vena cava and to drip in *slowly* 50 per cent glucose solution (1 L. in twenty-four hours supplies 2000 calories). With regard to protein, intravenous therapy with salt-poor human albumin is expensive and the danger of infection with serum hepatitis is always present when plasma

is used Plasma protein substitutes (dextran and P V P, polyvinyl pyrrolidone) have no nutritional value Quantitatively, whole blood is a very poor source of calories, of protein, and of other nutrients! It should not be used for intravenous feeding! On the other hand, 2 L of poor sa 5 per cent amino acid mixtures with or without added glucose will easil supply the daily requirement of nitrogen for tissue repair in most patient who cannot or who should not (see Hepatic Coma Syndrome) take protein by mouth

Intravenous alimentation should always be covered by intravenous or intramuscular administration of all vitamins given at the therapeutic level (p 535) The parenteral administration or withholding of sodium, potassium and magnesium ions depends on the clinical situation For instance in hepatitis with edema, sodium chloride-containing solutions should not be used, while during the diuretic phase of acute renal necrosis (lower nephron nephrosis) in hepatitis, large amounts of electrolytes may have to be given

THE HEPATIC COMA SYNDROME

Physicians from Galen s age to ours have recognized a connection between hepatic dysfunction and cerebral function Kinnear Wilson was the first to describe pathologic lesions of the brain in patients ill with cirrhosis but as yet no histologic abnormalities have been observed in the brains of patients who have died from hepatic coma which can be stated to be the cause of the neurologic and psychic manifestations of liver disease The lesions are probably metapathic, the result of biochemical changes

The manifestations of pre-coma and coma have been clarified by the recent clinical observations of Walshe[16,37] Adams,[1,2,23] Davidson,[0,27,29,30,31] Sherlock,[28] and their colleagues Walshe describes as part of the clinical picture of coma confusion apathy, personality changes spasticity, muscle spasms, choreiform movements athetoid postures, lead pipe and cogwheel rigidity of the arms flexion withdrawal of the legs, and cholemic crying Ankle clonus with plantar flexor Babinski responses was rather characteristic

Adams and Foley have clarified the diagnosis of pre- or impending hepatic coma by clinical and electroencephalographic findings

"The change in mental status was usually the first abnormal sign noted and frequently was recognized as an empty stare together with a lack of personal tidiness It was difficult to reach the patient in conversation, and remarks often had to be repeated As consciousness became more clouded some patients manifested confusion and grossly inappropriate behavior They performed acts very clumsily and had difficulty following directions but usually claimed a feeling of well being

"Occurring in close conjunction with the mental abnormalities was a characteristic tremor, which was absent at rest and developed on active maintenance of posture This was most satisfactorily demonstrated if the patient held his arms forward with hands and fingers extended In this way, the tremor was seen as an irregular, coarse flexion-extension movement at the metacarpophalangeal and wrist joints sometimes more marked on one side which when more severe involved the elbows and shoulders It is commonly referred to as the 'flapping tremor'

'The electroencephalographic changes show bilaterally slow waves of two-per second frequency that in the early stages occur in bursts, usually separated by cortical alpha rhythm The bursts appear at first in the frontal regions, but later increase in duration and spread laterally and posteriorly until the entire record is of slow activity '

The neurologic findings described are not uncommonly complicated in hepatic coma by delirium tremens in the alcoholic by hemorrhage into the brain as a result of prothrombin or fibrinogen deficiency, by other types of hemorrhagic disturbances, such as scurvy, and by Wernicke's encephalopathy, presently thought to be the result of thiamine deficiency

The neurologic signs and symptoms of hepatic coma and pre coma have been observed in Eck fistula dogs given meat in patients with porta caval or porta renal shunts in patients with portal vein occlusion and in patients with a wide variety of hepatic disorders ranging from Chiari's syndrome to acute hepatitis In many of these persons, attacks have been precipitated by oral feedings of meat high protein diets casein hydrolysates, amino acid mixtures, amino acids ammonium chloride ammonium citrate, urea, and cation exchange resins containing ammonium

It also appears that methionine or amino acid mixtures given by mouth will regularly precipitate neurologic signs in some patients ill with liver disease but these substances will not cause the signs to appear when they are given intravenously It has also been shown that sterilization of the bowel with antibiotics will inhibit the neurologic ill effects of a high protein diet in patients who are in a state of impending coma The observations and data on hand suggest that nitrogenous substances from the bowel—presumably the result of bacterial action on protein foods or nitrogenous chemicals—produce the neurologic and mental changes described above This can occur when blood is shunted directly from the portal system into the systemic system, even in the presence of normal hepatic function—the toxic substance being carried directly from the bowel to the brain (portal-systemic encephalopathy of Sherlock) The hepatic coma syndrome is more commonly seen when the liver is damaged Presumably the healthy liver detoxifies or utilizes the toxic nitrogenous material as it passes up the portal vein When the hepatic cells are damaged (anoxia fatty infiltration infection, etc) or when vascular shunts develop within the liver the toxic nitrogenous materials also pass into the systemic blood stream

TREATMENT OF HEPATIC COMA AND PRE COMA

Consumption of high protein diet is recognized as an essential part of the therapy of many forms of liver disease yet this may precipitate hepatic coma In handling patients with liver disease through diet therapy, the physician is making the patient walk a tightrope On the one hand he may push the patient into hepatic coma with too much protein, and on the other the patient s illness may be prolonged by prescription of a diet too low in protein A proper balance can be achieved by dietary juggling Diet therapy in liver disease should not provide, by mouth more than 2 gm of

protein per kg per day, and usually 1.5 gm per kg per day will suffice for adults. Patients on this diet should be observed each day for symptoms or signs of impending coma. At each visit to the sick room the patient should be asked to cock up his hands. If "flapping tremor" or other indications of pre-coma are noted, the diet prescription should be changed immediately to a low protein diet containing less than 40 gm. of protein but, providing as much animal protein as possible. This diet should continue until all symptoms and signs of impending coma have disappeared, at this time the patient may be switched back to his previous diet.

Present data indicate that intravenous, salt poor, amino-acid solutions are well tolerated in impending coma, and if the low protein diet has to be consumed for more than four or five days, *intravenous* infusions of amino-acid solutions may be used to bring the daily nitrogen requirements up to normal. Parenteral synthetic B-complex vitamins, as well as crude extracts of liver or yeast should be given each day. If the patient cannot eat, nutrition must be maintained by oral drip feedings of non-protein foods (glucose and fat) and/or parenteral carbohydrates and amino acid mixtures (see section on Tube Feeding and Intravenous Feedings, Chapters 21 and 32).

It is not certain at this time whether it is necessary to use antibiotic compounds to sterilize the bowel of patients in pre-coma. Clinical trials of a mixture of poorly-absorbed antibiotics are underway in our clinic for treatment of patients with the hepatic coma syndrome including patients who have had severe gastro intestinal hemorrhage. The oral antibiotic tablets which we are using contain Streptomycin Sulfate, Bacitracin, and Polymixin B Sulfate.

THE FATTY LIVER

The association of fatty liver with pellagra, with starvation, with diseases of inanition—such as ulcerative colitis and tuberculosis—and with alcoholism, is well known. From the studies of Connor[17] and Davies we accept the fact that the fatty liver is the forerunner of some forms of dietary cirrhosis, of tropical cirrhosis, and of alcoholic Laennec's cirrhosis. Although the exact progression to cirrhosis from the fatty liver is still cloaked in mystery, Davidson[15] and Zimmerman have proposed a reasonable account of its natural history and of its progression to Laennec's cirrhosis. Recent studies in Africa and elsewhere would seem to indicate that in man cirrhosis may not develop as a result of nutritional deficiency (see Kwashiorkor below). Should this be correct, it would seem that cirrhosis of the liver associated with alcoholism and other nutritional disturbances such as ulcerative colitis may not be the result of nutritional deficiency, but could be due to toxic factors which cause hepatic cellular necrosis, and autoimmune responses which produce further damage.

KWASHIORKOR

Until recently, Western physicians did not recognize that primary malnutrition—due to an unbalanced diet—produced fatty liver disease in man as it does in the laboratory animal. As a result of clinical studies in

the past two decades, it has become clear that primary, nutritional, fatty liver disease is widespread in the tropics and is perhaps, after caloric deficiency, the most common nutritional disease of man

This primary nutritional liver disease is most commonly seen in children and adults who live on cereal diets For example, the Africans develop a wide variety of nutritional disturbances, on cereal diets, which go by the name "Kwashiorkor" and which always involve the liver

Kwashiorkor is a disease of widespread tropical geographic distribution Case have been found in Mexico, Brazil, Africa and India, and occasional cases have been reported from Europe during famines (Mehlnahrschaden) It is rare in the United States We reported a case[34] in a ten month old Negro child in Chicago in 1950, and Davies, who examined the collected pathologic material at Duke University in North Carolina in 1949, found only 1 case among the children who had been autopsied at Duke University in the past twenty years The name "Kwashiorkor" means "red boy" and is derived from the characteristic associated dermatitis One African tribe has a name for the disease which has intrigued my Freudian psychiatric colleagues When translated, it means, "the disease-the-first-child-gets-when-the-second child is-born" This name is understandable when the usual tribal custom of weaning the child at the age of three is pointed out However, Kwashiorkor is *not* the result of parental rejection It is a nutritional deficiency which develops after weaning because the child can get no more milk and has to live on a pure carbohydrate diet The cereals consumed by the children, such as manioc (cassava) contain, at the most, 2 per cent protein as compared to the 13 per cent protein content of wheat Children from certain tribes living in endemic areas appear immune to this disease Analysis of their eating habits reveals that some of these children drink cow's blood as part of their diet while others eat fish habits which are not shared by the children of affected tribes

Malaria, schistosomiasis, amebiasis, and other infestations are rampant in the areas where Kwashiorkor exists, and has been considered to be an associated etiologic cause of Kwashiorkor However, Nichols has studied the relationship between parasites, dietary intake and liver disease in West Africans and presents data which indicate that dietary deficiency is the sole cause of liver involvement in Kwashiorkor He indicates that it is not aggravated by concomitant parasitic infestation

In general it is felt that protein deficiency is the cause of Kwashiorkor and this disease has recently been defined as "A state of ill health occurring where diets are habitually poor in good quality protein, while they are more nearly adequate in calories It includes deficiency of protein foods imbalance of amino acids and deficiency of accessory food factors associated with protein metabolism It is more easily recognized when caloric intakes have been relatively high from the use of starchy foods" Gyorgy has recently described a nutritional factor found in human milk the bifidus factor" deficiency of which may also be related to the development of Kwashiorkor

The early symptoms of this disease include apathy, edema umbilical hernias, potbellies and later, changes in the hair and in the skin The

normally curly, coarse hair becomes fine, thin, and reddish yellow, tufts of alopecia appear, and the jet black skin of the native becomes reticulated It peels and a patchy black-and-white surface remains The skin looks like black paint which has flaked off woodwork The salivary and lachrymal glands enlarge The tongue becomes edematous, smooth, and easily in dented The pancreas is involved Peristalsis is increased, and greasy, slimy stools are passed Other findings include anemia, neurologic changes similar to those of beriberi, and paraesthesias Death usually occurs from acute dysentery, tuberculosis, or pneumonia [3]

In the adult, the residues include cirrhosis of the liver in many but not all tribes Primary hepatoma of the liver is common and may be related to riboflavin deficiency Other late manifestations include carcinomas of the male breast, salivary gland, and reticulo endothelial system Endomyocardial fibrosis may be part of the syndrome Hemosiderosis of the liver and other organs is present in South African cases

Treatment —Although prevention is the aim of therapy, this ideal is difficult to attain in tropical countries where leached soils, poverty, ignorance, and custom lead to primitive animal husbandry and animal protein malnutrition in man

Once Kwashiorkor has developed, the gastrointestinal tract seems unable to handle animal proteins such as meat, fish, or eggs This may be due to lack of formation of the proper enzyme systems for digestion of these foods, or it may be the result of increased gastrointestinal permeability The latter lesion may allow direct absorption of complete proteins from the gut into the blood stream, and this may produce severe immunologic reactions Be this as it may, children with Kwashiorkor respond well to therapy with milk, which should be used to restore their protein tissue mass to normal before other animal protein foods are added to the diet Naturally, associated diarrheal and parasitic infiltrations must be treated The value of dried, powdered stomach preparations and of vitamin and amino-acid supplementary therapy in this disease needs further study

TOXIC HEPATITIS AND CIRRHOSIS

Opie and others have clearly indicated that the repair of hepatic damage by toxic agents, such as carbon tetrachloride, is enhanced by diet therapy Toxic hepatitis seems to have become more common recently as a result of the increasing use of organic solvents in industry and in the home Iatrogenic toxic hepatitis may be the result of endocrine therapy (methyl testosterone jaundice), psychotherapy (chlorpromazine jaundice), and antimicrobial therapy (arsenic jaundice) among others Acute toxic hepatitis should be managed on regimens suitable for patients with infectious hepatitis, and those ill with chronic toxic hepatitis or cirrhosis should be treated as are patients with Laennec's cirrhosis

The development of toxic liver diseases other than those described above has also been related to nutritional factors Senecio cirrhosis is seen in white and native populations in South Africa It is the result of eating bread and other foods made from flour contaminated with the crushed

seeds of *Senecio aureus* a plant which grows in the wheat fields of the Cape Province In North America Senecio poisoning is one cause of cirrhosis in cattle Selzer and her colleagues have shown that Senecio cirrhosis develops in rats only when the weed is added to an experimental diet poor in protein An adequate protein intake protects the animals These experiments may bear on the problem of infantile hepatic necrosis in Indians, and on Jamaican infantile veno-occlusive hepatitis which resembles Senecio cirrhosis and which occurs in weanlings living on low protein diets and fed decoctions of local plants [9]

CIRRHOSIS AND FIBROSIS OF THE LIVER[33]

Cirrhosis of the liver is a common disease in the tropics, in those who are alcoholics and in individuals who have had attacks of viral hepatitis It also develops—but much more rarely—in patients suffering with a wide variety of disorders, such as hemochromatosis, biliary cirrhosis, cholangiolitic jaundice and hepato lenticular degeneration It may appear after infection with brucella abortis, spirochetes, and amoebæ, after infestation with schistosomes or as a result of metabolic or cardiac diseases While diet therapy is used to treat the cirrhosis which develops in all these conditions, outstanding success is not attained in all instances It is true that nearly all alcoholics who are ill with Laennec s cirrhosis can be restored to, and kept in good health by diet therapy, provided that they do not drink Among the remainder, far too many patients with cirrhosis progress slowly or rapidly towards death in hepatic failure or as a result of rupture of the esophageal varices, for us to be too sanguine about the long-term results of present day diet therapy Nevertheless manipulations of diet have constituted a major advance in our attack on the problem Diet therapy is only one part of the therapeutic regimens found to be of benefit for patients ill with cirrhosis In essence the regimen consists of bed rest, absolute prohibition of all forms of alcohol protection of the patient from hepato toxic drugs and chemicals, and provision of a diet rich in protein, calories and natural nutrients Salt or sodium restriction is used when necessary Supplementations to the diet of salt substitutes and intravenous and water-soluble vitamins are made as indicated Particular attention is paid to actual daily dietary intake, to simple supportive psychotherapy, and to the daily weight of the patient When specific deficiencies co-exist with cirrhosis the patients should be treated immediately with a good diet and intramuscular water-soluble vitamins After the lesions have gone away extra vitamins are not necessary to treat the cirrhosis, if a well balanced diet is consumed each day

Manipulations of the diet must be made in accordance with the clinical state of the patient For example, development of impending coma must be met by a sharp reduction of protein to less than 40 gm per day, while rupture of an esophageal varix requires the use of massive blood transfusions and parenteral alimentation

Klatskin and Gabuzda have shown that marked improvement occurs in cirrhotic patients when they are placed on a minimal dietary regimen (1 gm protein per kg body weight per day) In our hands improvement

of patients on a minimal dietary regimen in a metabolic ward takes place rather slowly over a period of twenty to sixty days At that time they enter into a "steady state," and then there seems to be no further improvement When they are in the "steady state," one can study the effects of other nutrients (such as intravenous salt-free human serum albumin, methionine, B complex vitamins, etc) added to the minimal dietary regimen If these are beneficial, their value will be indicated by the development of a continued positive nitrogen balance during the test period which does not rebound when supplementary therapy ceases [5]

In our hands intravenous albumin, methionine, choline, the B complex vitamins, and intraheptol do not seem to confer any special benefits when tested as described above in cirrhotics However, extra amounts of protein by mouth or intravenous amino-acid mixtures (up to 2 gm per kg per day) are beneficial as they produce a sustained positive nitrogen balance and speed recovery

With regard to the treatment of cirrhosis in alcoholics, preventive teetotalism must be the goal of all who deal with the chronic alcoholic

Dietary Treatment of Edema and Ascites in Cirrhosis —Hidden water retention, frank edema, and ascites are common complications of cirrhosis [11] They are usually associated with nutritional endocrinologic, and secondary metabolic disorders The signs of malnutrition commonly seen are loss of flesh and a raw, beefy tongue—both due to protein wastage—scurvy, pellagra, cheilosis, and other signs of B complex deficiency Endocrinologic changes consist in the main of spider nevi, liver palms, loss of libido, testicular and prostatic atrophy, loss of hair on the chest, gynecomastia, and amenorrhea, or menorrhagia These latter findings are related to the lack of production of hormones due to malnutrition and also to the inability of the damaged liver to conjugate and deactivate normally circulating hormones Metabolic defects are hypoalbuminemia, depressed levels of prothrombin and cholinesterase in the serum, and electrolyte imbalance The retention of water has been related to raised portal *pressure, increased anti-diuretic hormone, secondary aldosteronism,* hypoalbuminemia, and tissue permeability defects, among others Be that as it may, an essential difficulty in ascites and edema is the increased reabsorption of sodium by the kidney tubules, which is followed by tissue binding of sodium and water Restriction of dietary sodium to levels less than that lost by the body from the skin, stool, and urine, allows the kidney to lose bound water with the sodium it excretes This eventually reduces the water logging Repair of tissue mass is also associated with a slow, steady loss of excess water as the restoration of protein nutrition moves the patient's tissues from depletion towards the normal state With tissue repair, a long-term slow, steady diuresis occurs, and eventually the kidney is once again able to handle the sodium load of a normal salt containing diet [7]

Restriction of Sodium —In our hands, restriction of sodium has been a most useful procedure in the delivery of ascitic and edema fluid, in preventing the re-accumulation of ascites following paracentesis, and in restoration of tissue in malnourished cirrhotics The difficulties encountered in therapy are mainly economic, for repair of tissue wasting and restoration

of hepatic integrity may take many months, which should be spent in bed—preferably in a hospital In addition, the diet is made up of expensive protein foods, some of which have to be processed commercially to remove sodium The restriction of sodium in the diet is an onerous burden for the dietician, and the food which is served is all too often found to be flat tasting or unpalatable

Generally speaking restriction of sodium need not be severe to achieve good results In most instances, diets containing between 20 and 40 mEq of sodium per day (approximately 1 1 to 2 3 gm of NaCl per day) will keep the cirrhotic 'dry' after paracentesis Nevertheless, there does seem to be a critical level of sodium intake for each individual patient above which water accumulates in tissues or in the peritoneal cavity We have not been able to correlate this critical level of sodium intake with any measurement made in our patients but suspect it is related to the patient's tissue protein status, *i e* the more depleted the patient's tissues of protein, the lower the sodium intake required to prevent water logging It is, therefore, wise to start therapy, if possible with a rather rigid diet providing 25 mEq or less of sodium per day and thereafter if the patient remains 'dry' to increase the salt intake to the limits of tolerance, as shown by rapid or uncontrolled gain of weight or by reaccumulation of fluid The more sodium added to the diet, the greater the rate and amount of water retained

Hidden sources of sodium in intravenously administered plasma and whole blood (sodium citrate) transfusions or in the diet—such as is contained in bread or drinking water which has been artificially softened—may cause an unexpected re-accumulation of fluid in patients who are 'dry'

An instance of the effects of adding sodium to the diet is shown in an experiment on the cirrhotic patient J D (Fig 58) in which 10 gm of salt were added each day for three days to his low sodium diet at a time when he was 'dry' and when his weight was steady As a result of this, he gained 5 pounds of weight in four days and it took a week for him to lose this extra water bound in his body by the excess sodium The rapid weight gain induced by deliberate salting during therapy with low sodium diets and the length of time required to restore equilibrium are exceedingly useful methods for demonstrating to the individual patient the good effects of a low sodium regimen and the ill effects of straying from the regimen It is suggested that the physician demonstrate to the patient and his family the value of sodium restriction by deliberate salting of diets for short periods of time

To control the level of sodium intake in the diet it is necessary to weigh the patient each day or to have him weigh himself, preferably the first thing in the morning These weights should be charted Rapid gain in body weight means that water is accumulating because of sodium retention and too much sodium in the diet On the other hand a slow, steady gain of weight which is associated with clinical improvement is usually due to restoration of tissue mass Very rarely, rapid gain in body water and body weight is the result of "low salt syndrome" (see page 66[illegible])

When patients have been on the low salt high protein diet for some months and when clinical improvement is obvious the daily output of

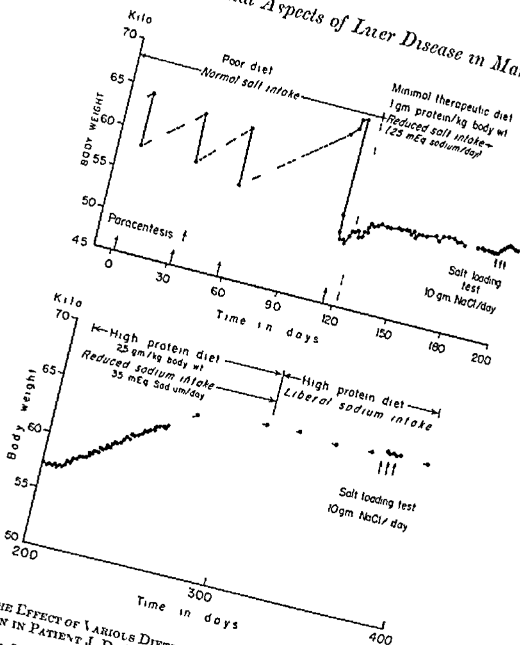


Fig 58 —The Effect of Various Diets on Body Weight and Ascitic Fluid Accumulation in Patient J D Ill with Alcoholism, Cirrhosis, and Ascites

1 From day 0 to day 110 patient was treated at home by repeated paracenteses At this time his diet was poor he had a normal salt intake and he re accumulated fluid rapidly

2 On day 111, a paracentesis was done and he began to re-accumulate water He was placed on a minimal therapeutic diet (1 gm of protein per kilogram body weight and basal plus 150 per cent calories) Sodium was reduced to 25 mEq per day On this regimen he stopped collecting fluid but did not gain weight On day 180 a salt-loading test was started He was unable to handle sodium and re-accumulate water

3 On day 200 the diet was changed by increasing the protein to 2 5 gm per kg body weight per day This addition of protein raised the sodium intake to 35 mEq per day On this regimen there was a rapid restoration of body tissue with reduction in liver size Spider nevi disappeared The steady gain in tissue was associated with a constant loss of water

4 On day 410 his regimen was changed to a diet containing liberal amounts of salt He did not gain water, and on day 376 when a salt-loading test was administered there was no re-accumulation of water Restoration of tissue mass and regeneration of liver tissue allowed the kidney to handle sodium normally

sodium in their urine begins to increase, and eventually they can return to a diet containing moderate or normal quantities of salt The decision to increase the amount of sodium in the diet should be implemented by a trial of salt feeding and this must be controlled by daily weighing If for example 5 gm of salt are added each day to the diet and if the weight increases each day at a rapid rate, then the patient has not recovered his ability to excrete sodium and to handle the excess salt Obviously he must remain on his low sodium diet for a further period of therapy until it is considered wise to attempt a second trial of salt feeding Measurement of twenty-four hour urinary sodium excretion may be worthwhile at this time

Hazards of Sodium Restriction —Sodium restriction may not be without hazard In those patients in whom chronic renal disease co exists with cirrhosis, the untoward manifestations of severe sodium depletion are the result of high urinary output and failure of the kidneys to reabsorb sodium In such patients sodium is removed from the body at a relatively faster rate than water The blood plasma and extracellular fluid become hypotonic, presumably the tissues lose potassium, the individual cells are damaged sodium enters the cell from the extracellular space and an acute cellular hydration develops The patient subject to continued loss of electrolytes becomes weak and lethargic If the electrolyte loss is not corrected, he now becomes confused and may have convulsions Muscular cramps and pain—especially abdominal pain or cramps—often occur early during the development of the 'low salt syndrome ' In these patients serum sodium is usually low (below 130 mEq sodium per L of serum) the blood urea rises, and the carbon dioxide combining power of the plasma drops The patient eventually dies in uremia if not treated with hypertonic saline infusions The exact part played by potassium disturbances in this syndrome has not been clarified

A similar syndrome has been reported in cirrhotic patients who, while living on a low salt diet, are treated with repeated injections of mercurial diuretics and repeated paracenteses These patients do not suffer from chronic renal disease In them total body sodium is low as a result of the diet, and the extra loss of electrolyte occasioned by repeated diuresis and paracentesis further depletes the body stores These patients repeatedly "bleed' electrolyte from tissues into the peritoneal cavity whence it is removed Eventually cellular overhydration develops with generalized hypotonicity of the body fluids and a low-salt or low electrolyte syndrome appears

Restoration of salt balance in cirrhotic patients suspected of having the low salt syndrome should be made by vigorous infusions of hypertonic saline which will 'pull" water from overhydrated cells into the circulation All food or fluids by mouth or by vein should be stopped and initially, 2 l of 3 per cent saline should be given slowly Its effects are followed by close observation of hematocrit urine output and sodium levels If isotonic or hypotonic solutions are given while the hypertonic saline is *running into* the circulation or if glucose is infused under the circumstances described above, the infused water and salt will distribute themselves evenly throughout the body and worsen the edema and the metabolic upset

In view of the dangers of salt depletion, it is most important to test renal function before initiating low sodium diet therapy in cirrhotics When the dietary regimen is started, measurements of nonprotein nitrogen—and when possible, plasma carbon dioxide combining power and serum sodium and potassium—should be made at least once a week for the first few weeks after treatment has been instituted The physician should watch for the development of cramps, abdominal pain, or unusual drowsiness

If renal function is moderately disturbed, salt restriction may be instituted, but starting rather cautiously and allowing an initial intake of between 50 and 60 mEq of sodium per day, thereafter increasing or decreasing the sodium intake as indicated by changes in body weight, urine output, the clinical conditions of the patients, and biochemical data Mercurial diuretics should never be used under such circumstances

Nutrient Intake with the Low Sodium Diet —Most patients ill with cirrhosis, and especially those who have ascites, show the ill effects of long continued protein and caloric starvation In them, part of the cellular protein has been replaced by water and possibly by electrolytes This chronic cellular water logging is clinically occult, but contributes to edema and ascites when they develop Although the concept of "hunger edema" associated with cirrhosis may explain in part why sodium is retained in clinically water logged cirrhotics, the fact remains that with low sodium and high protein intakes even non-edematous cirrhotics deliver water and salt and lay down tissue protein Nevertheless, patients ill with cirrhosis improve, but slowly on a so-called minimal diet which is "well balanced" by present concepts, but which provides only 1 gm of protein per kg of body weight

The value of a high protein, high caloric diet which is low in sodium is that clinical improvement is much more rapid and sustained than with the minimal diet The disadvantages of the diet have been described above Our experiences suggest that a low sodium diet, providing basal caloric requirements—plus a further 60 to 100 per cent of required calories 2 gm of protein per kg body weight, 30 per cent of the calories as fat, and the remainder of the calories as carbohydrates—can be consumed by the average patient without difficulty Sample diets which we have used are shown below These provide from natural sources approximately 5 gm of methionine, 90 mg of ascorbic acid, 20 mg of niacin, 5 mg of riboflavin, and 3 mg of thiamine per day

When a nutritionally well-balanced, low sodium high protein diet is offered and consumed day after day by the cirrhotic patient, supplementation of the diet with choline, methionine, and vitamins is not necessary In our hands, intravenous injection of liver extracts has not been of outstanding value in the management of cirrhotic patients Its exact usefulness awaits further evaluation When patients with cirrhosis present themselves initially for examination, they are often quite ill with vitamin deficiency syndromes, but these are not as commonly seen now as in the pre war years When deficiency states are noted, treatment with water soluble vitamins should be vigorous It is our custom when we diagnose vitamin deficiencies in our cirrhotic patients to give two intramuscular injections of a water-soluble B complex mixture twice a day for the first week and

then to taper off with one injection per day for the next week One B complex vitamin capsule is also given by mouth 3 times a day for the first two weeks and then is discontinued when the patient is eating well

TABLE 77 —LOW SODIUM MILK SHAKE FEEDING

200 ml water (distilled)
50 gm Lonalac
50 gm Protinal

Sodium content 23 mg
Protein content 40 gm
Cost 31 cents

TABLE 78 – SOME SOURCES OF SODIUM TO BE AVOIDED*

Cereals —Bread crackers pretzels, baked goods and most breakfast cereals

Meat and Fish —All shellfish processed meats and fish especially ham bacon salt pork, frankfurters sausage cold cuts corned beef salt fish canned fish and meats, bacon fat, bouillon cubes meat extracts consommes pickled meat and fish

Dairy Products —Cheese, canned soups milk butter margarine ice cream white of eggs

Vegetables —Celery beets beet greens spinach canned beans sauerkraut and other pickled vegetables Most canned vegetables Frozen peas

Water —Some city waters Water treated in softening equipment

Miscellaneous —Olives pickles catsup sauces salad dressings mayonnaise popcorn salted nuts candy and candy bars peanut butter yeast and yeast ex tract packaged flavored gelatin desserts chewing tobacco sodium glutamate (soy sauce) Celery salt garlic salt, table salt sodium salts of drugs bicarbonate of soda self rising flour and flour mixes Blood transfusion (sodium citrate) blood plasma infusion

* See (1) Sodium and Potassium Analyses of Food and Waters and (2) ' The 200 mg Sodium Diet Outline and Food Lists prepared by Dr Charles E Bills Mead Johnson & Co Evansville Indiana

Tables 77 78 and 79 from Kark courtesy of Med Clin North America *35* 73, 1951

When by clinical observation tissue wasting is severe or when the patient is unable or unwilling to eat, it has been our custom to supplement the maximal oral protein intake by infusion of sodium free or low sodium intravenous amino acid mixtures, twice each day for the first two weeks or the first month of treatment These are infused at the rate of 1 L in two hours or longer When patients have not been able to stay in hospital for prolonged care because of their social or economic problems, amino acid infusions have been given to them during the weekends This is done once on Friday night after work and twice each day on Saturday and Sunday, the patient remaining in bed during this time These weekly in fusions in bed ensure that the patient has at least two days of high protein intake per week and a certain modicum of rest Moreover he is removed from the temptation of alcohol at weekend parties

Preparation of the Diet —Fresh meats and fish contain fair but not excessive quantities of sodium Beef, veal, fresh pork, salmon, and halibut

all contain approximately 50 mg of sodium per 100 gm of flesh (approximately 20 gm of protein) Most cheeses contain excessive quantities of salt, as do most other milk products Generally speaking, all processed meats, fish and meat products, and canned vegetables contain excessive quantities of salt Tables 78 and 79 give lists of foods which are high and fairly low in salt

TABLE 79 —SOME FOODSTUFFS LOW IN SODIUM CONTENT

Breakfast Cereals

Most ready to-serve breakfast cereals are salted, some heavily Cereals in the following list are low in salt

Barley pearled	Pettijohn s
Corn meal	Puffed Rice
Cracked wheat	Puffed Wheat
Farina plain	Rice
Instant Ralston	Shredded Wheat
Maltex	Wheat germ
Oatmeal (rolled oats)	Wheatena

Breads Bread Substitutes and Spreads

The following are low in salt

Breads and substitutes	*Spreads*
Low sodium bread (see recipe below)	Unsalted butter
Low sodium caraway seed bread	Jam
Low sodium cinnamon roll	Jelly
Passover bread (matzoth)	Marmalade
	Honey

All ordinary breads crackers and pastries contain considerable sodium from the use of salt and soda In the larger cities one may be able to locate a specialty baker who can supply bread without these ingredients Otherwise, if bread is used it must be specially baked The following recipe provides a bread of excellent flavor Loaf (Pound 16 slices)

Low sodium bread

Flour (Gold Medal)	2¼ cupfuls
Sugar	1½ level tblsp
Shortening (Spry)	1 level tblsp
Lonalac powder	3 level tblsp
Lukewarm water	7 ounces
Yeast	½ cake

Sift the flour and mix it with the sugar and shortening Mix the Lonalac powder and lukewarm water and add the crumbled yeast Add the Lonalac water and yeast mixture to the mixture of dry ingredients and shortening Stir with a spoon until a soft dough is formed (about 2 minutes) Turn out on a floured bread board and knead until the dough is elastic (about 15 minutes) Place in a greased bowl large enough to permit the dough to rise double in bulk Cover with a damp cloth and let rise 1 hour and 15 minutes in a warm place (86° F) Turn the sides of the dough towards the center, and punch out the gas Let rise 20 minutes in a warm place Turn the dough onto a floured bread board and mold into a loaf Place in a greased pan and let rise 1 hour in a warm place Bake in a 400° F oven for 40 minutes

Low Sodium Caraway Seed Bread —Add 2 level table poonfuls of caraway seed to the dry ingredients, then follow the above procedure

Low Sodium Cinnamon Roll —Mix thoroughly ½ cupful of sugar and 1 level tablespoonful of cinnamon powder After the 20 minute rising period of the above bread recipe, flatten the dough to an 18 inch length Sprinkle the sugar mixture on top of the dough and dot with 2 level tablespoonfuls of Spry Roll the sides of the dough together and pinch together to hold the sugar mixture in Cut into 3 lengths, and braid together Place in a greased pan and let rise again in a warm place Bake in a 400° F oven for 40 minutes

Matzoth —Patients who lack facilities for making low sodium bread may find an acceptable substitute in certain forms of matzoth or Passover bread This product frequently called matzos or Jewish crackers is usually sold in the form of large thin crackers It can be bought at kosher stores or by special arrangement from other grocers Originally all matzoth were unsalted but at the present time many varieties contain salt Matzoth marked for Passover or the kinds known as plain matzos' or thin tea matzos may be used all others should be avoided Matzoth are especially convenient for children and for adults who must carry their bread with them for eating away from home

Spreads —As a spread for low sodium bread or matzoth one may use jam, jelly, marmalade or honey Four squares of salted butter (or margarine) are allowed daily (Any other fat used must be unsalted) Do not use peanut butter or cheese spreads

Vegetables and Substitutes

All vegetables in the following list may be used freely when purchased fresh and when dried or frozen if so indicated Canned vegetables are almost always salted and should not be used Certain frozen vegetables such as peas are sometimes salted

Asparagus	Corn frozen	Potatoes sweet
Asparagus frozen	Cowpeas	Potatoes white
Beans green	Cucumber	Pumpkin
Beans green, frozen	Eggplant	Radishes
Beans, lima green	Endive	Rice
Beans navy, dried	Lettuce	Rutabagas
Broccoli	Macaroni	Soybeans
Brussels sprouts	Mushrooms	Soybeans dried
Brussels sprouts frozen	Okra	Spaghetti
Cabbage	Onions	Squash all kinds
Carrots	Parsley	Tomatoes
Cauliflower	Parsnips	Turnip leaves
Cauliflower frozen	Peas	Turnips white
Corn	Peppers	Turnips yellow

NOTE The following vegetables *should not be used* Celery beets, beet greens dandelion kale mustard greens spinach and sauerkraut

Salads —When vegetables are used in salads vinegar lemon juice salad oils and any of the permissible seasoning may be used Mixed dressings should be prepared at home, without salt Egg yolk (but not white) may be used in cooked dressing or mayonnaise In making gelatin salads use plain gelatin not flavored or acidulated gelatin dessert mixtures Cottage cheese made from Lonalac may be served with salads

Fruits and Fruit Juices

All fresh fruits (raw or cooked) and fruit juices may be eaten Canned dried or frozen fruits and juices may likewise be used (unless the label specifies that salt or sodium benzoate has been added)

Beverages

The following beverages may be used

- Apple juice
- Chocolate, with liquid Lonalac
- Coca Cola
- Cocoa Hershey's with liquid Lonalac (avoid Dutch process ' cocoa)
- Coffee
- Ginger ale
- Grape juice
- Grapefruit juice
- Lemonade
- Lonalac
- Orange Crush
- Orange juice
- Pineapple juice
- Postum
- Prune juice
- Tangerine juice
- Tea

Do not use water which has been run through water softening equipment

TABLE 80 —SOME FOODSTUFFS LOW IN SODIUM CONTENT—(*Continued*)

Desserts and Sweets

The following desserts and sweets may be used when prepared without salt or soda When eggs are called for in recipes use only the yolks The white of an egg contains much more sodium than the yolk, so that if whole eggs were used in desserts, the amount would have to be subtracted from the daily egg allowance

Desserts

- Rice cooked in liquid Lonalac with fruit and sugar
- Ice cream made with Lonalac
- Corn starch pudding made with Lonalac
- Gelatin desserts made with plain gelatin fruits and juices (*Do not* use prepared gelatin desserts or acidulated gelatin)
- Fruit pies made with unsalted crust
- Fruit tapioca pudding

Other sweets

- White sugar
- Jams, jellies marmalades
- Honey
- Homemade candies prepared with white sugar such as peppermint patties or fudge made with liquid Lonalac instead of milk
- Popcorn with syrup made of white sugar
- *Do not use brown sugar, molasses or syrups other than homemade* syrup prepared with white sugar

Condiments Flavorings, Fats and Oils, and Miscellaneous Foods

Condiments and flavorings The following may be used

- Allspice
- Caraway
- Cinnamon
- Curry powder
- Garlic
- Ginger
- Lemon extract
- Lemon juice
- Mace
- Mustard powder (not prepared mustard)
- Nutmeg
- Paprika
- Pepper black
- Pepper, red
- Pepper, white
- Poultry seasoning
- Sage
- Sugar white
- Thyme
- Turmeric
- Vanilla extract
- Vinegar
- Walnut extract

Do not use catsup, celery salt onion salt garlic salt meat flavoring, prepared horse radish, prepared mustard Worcestershire sauce

Fats and Oils —Unsalted fats such as lard, Spry and Crisco may be used *Do not* use salted butter or margarine except for the 4 squares specified in your diet outline *Avoid* all other salted fats such as bacon fat and other meat drippings

Miscellaneous Foods —Unsalted nuts Unsalted popcorn (the corn may be popped dry or with one of the unsalted fats mentioned above unsalted butter or syrup made with white sugar may be used for flavoring) *Avoid* pretzels potato chips pickles olives and all other salted or spiced foods

Table 81.—Some Low Sodium Menus Used in Treating Patients Ill with Chronic Liver Disease

(These menus provide a diet high in protein and low in salt)

Following is a sample of a five day rotation diet which provides 181 grams of protein 121 grams of fat 464 grams of carbohydrate and 0 9 grams of sodium

Day 1

Item	*Grams*
Breakfast	
Orange juice	100
Oatmeal (dry weight)	30
Salt free bread	50
Salt free butter	6
Combined	
Skim milk	100
Water	100
Lonalac	62
Jelly	15
Sugar	59
Black coffee	150
Dinner	
Salt-free beef	150
Salt free potato	100
Salt-free carrots	100
Salt-free bread	50
Jelly	15
Combined	
Skim milk	100
Water	100
Lonalac	70
Jello (dry weight)	30
Black coffee or tea	150

Item	*Grams*
Supper	
Eggs	100
Salt-free frozen peas	100
Fresh tomato	100
Salt-free cottage cheese	120
Salt free bread	50
Salt free butter	7
Combined	
Skim milk	100
Water	100
Lonalac	70
Banana	100
Jelly	15
Black coffee or tea	150
8 00 P M Nourishment	
Salt-free bread	50
Jelly	15
Combined	
Skim milk	100
Water	100
Lonalac	70

Day 2

Item	*Grams*
Breakfast	
Orange juice	100
Muffets	20
Salt-free bread	50
Salt-free butter	10
Combined	
Skim milk	100
Water	100
Lonalac	70
Jelly	15
Sugar	82
Black coffee	150
Dinner	
Salt free beef	100
Rice (dry weight)	30
Salt free cottage cheese	80
Salt-free bread	50
Salt-free butter	6
Combined	
Skim milk	100
Water	100
Lonalac	65
Jello (dry weight)	30
Jelly	15
Black coffee, or tea	150

Item	*Grams*
Supper	
Salt-free veal	100
Eggs	100
Salt-free frozen green beans	100
Fresh tomato	100
Salt free cottage cheese	50
Salt-free bread	50
Salt free butter	3
Combined	
Skim milk	100
Water	100
Lonalac	80
Prunes (with pits)	80
Jelly	15
Black coffee or tea	15
8 00 P M Nourishment	
Salt-free bread	50
Jelly	15
Combined	
Skim milk	100
Water	100
Lonalac	65

quantity of bile, the motility of the gallbladder, and the tone of the sphincter of Oddi Moreover, the bile is essential for proper absorption of fats, fat-soluble vitamins and a number of hormones and metabolic substances which cycle through the entero-hepatic circulation during consumption and digestion of food However, it is surprising to find that only 5 to 10 per cent of patients with gall stones are dyspeptic

Effects of Diet on the Biliary Tract and Bile —High protein diets and, to a lesser extent, high fat diets increase bile production Dehydration and high carbohydrate diets decrease bile formation Fatty food cholagogues—such as cream, egg yolk, and olive oil—cause the sphincter of Oddi to relax and initiate contraction of the gallbladder This process is thought to be initiated by food through the hormone, cholecystokinin, which is released from the upper intestinal wall into the blood stream and is carried to the gallbladder and sphincter of Oddi Thus at mealtimes a store of gallbladder bile is released into the duodenum when it is most needed to help in the digestion and absorption of fats

Many clinicians suspect that aberrations of this mechanism are responsible for initiating biliary or pancreatic disorders It has been postulated that following large meals high in fat and protein the gallbladder may contract against an unrelaxed sphincter of Oddi (achalasia of the sphincter of Oddi) or against a spastic sphincter of Oddi (biliary dyskinesia) This may result in acute or recurrent biliary colic, and obstructive jaundice may develop If an anomalous pancreatic duct opens directly into the biliary duct then when the situation described above develops, bile may regurgitate into the pancreas, and acute or relapsing chronic pancreatitis may ensue

Nutrition and the Development of Gall Stones and Cholecystitis — Recent studies have clearly demonstrated that neither bile nor gall stones nor gallbladder wall from patients with gall stones or cholecystitis are infected with organisms This and other investigations strengthen the concept that cholecystitis is not an infectious disease, but is the result of a chemical inflammation of the wall of the gallbladder Thus it seems that the genesis of cholecystitis and gall stones (except pigment stones resulting from hemolytic phenomena) must be sought for in that rather vague but important field of medical endeavor which relates body build, race, and other genetic factors to environmental, endocrinologic, and nutritional abnormalities Cholecystitis—and in particular, gall stones—varies in incidence from country to country, appears to be high in those who live on a high calorie, high-fat diet, is rarely seen among the Japanese is common in Jewish people, appears in families, develops in parous women, especially if they are obese and fair becomes troublesome at the menopause and occurs more commonly in females than in males The development of cholecystitis and gall stones appears to be related to cardiovascular disease, to familial hypercholesterolemia, to pancreatic disease, and to diabetes

While there is no proof at present that dietary habits are the prime cause of cholecystitis and gall stones, the data collected thus far are highly suggestive What is needed are world-wide studies on the incidence of gallbladder diseases in populations consuming different diets—studies which

would be similar to those made by Ancel Keys on different populations in different parts of the world which relate degenerative heart disease with high fat diets and high blood cholesterol levels.

Dietary Management of Patients with Dyspepsia, Gall Stones, and Cholecystitis.—There is no evidence that food containing cholesterol *per se* has any appreciable effect on the amount of cholesterol excreted by the hepatic cells. Consequently, a cholesterol free diet cannot be regarded as a means of preventing gall stones. On the other hand, prescription of a low fat containing diet is a time honored dietary regimen for patients with chronic flatulent dyspepsia who have in addition physical signs or radiologic evidence of chronic cholecystitis or gall stones. Greasy or fried foods, eggs, mayonnaise, salad dressings, cheese and pork products, and high fat containing pastries rich in cream or suet should be avoided. Many patients recognize that they cannot tolerate onions, sauerkraut, cabbage, radishes, turnips, cucumbers and spicy foods such as chili con carne and curry. Vegetable fats, such as olive oil or corn oil which are rather unsaturated, seem to be beneficial when the gallbladder is functioning normally, as they stimulate bile flow. Their employment in the regimen must depend on the patient's ability to tolerate them.

When acute cholecystitis develops, no fried food should be given by mouth, and the patient should be fed parenterally (see pages 607 and 655, on parenteral feeding. Immediately after an acute attack, the diet should limited to small amounts of carbohydrate foodstuffs such as fruit juices, pureed potatoes, rice and tapioca. Later, more solid cereals can be added, together with skim milk, broiled fish, and lean broiled meats. Non-fat white chicken or turkey meat may also be employed.

Chronic Obstructive Jaundice.—Chronic obstructive jaundice is most commonly seen as a result of post-operative traumatic stricture of the bile ducts, congenital lesions of the bile ducts, undetected calculi, undetected slow growing carcinoma of the hepatic ducts, cysts in the head of the pancreas, biliary cirrhosis, and cholangiolitis. In all these lesions, the nutrition and metabolism of the body is disturbed by acholia. In essence the main pathophysiological disturbance is steatorrhea with resulting malnutrition due to loss of calories, vitamins, and minerals. Loss of dietary calories raises the demand for calories from protein sources with resultant development of fatty liver and impaired production of plasma proteins. Failure to absorb vitamin K produces prothrombin deficiency manifested by needle puncture hematomata, spontaneous bruising, and a hemorrhagic tendency. The loss of calcium and vitamin D produces osteomalacia with demineralized bone, kyphosis, fractures, collapse of vertebræ, and herniation of the intervertebral disc into the vertebral bodies (Schmorl's nodes). In addition osteoporosis may be present, perhaps due to protein deficiency and reduced steroid output as a result of malnutrition. Vitamin A deficiency produces night blindness and hyperkeratosis while failure of absorption of unsaturated fatty acids may result in eczematous-like skin lesions. Vitamin E deficiency may produce muscle weakness. Loss of potassium may cause potassium nephropathy, atony of the bowel, and typical muscle weakness.

Prevention of the ill effects of chronic obstructive jaundice consists of providing a regimen high in calories and rich in protein Little advantage is gained by giving more than 2 grams or protein per kilogram body weight Fat is poorly tolerated and badly absorbed and should be limited to 40 grams daily Unsaturated fat such as corn oil may be used on salads Fat soluble vitamins should be given at therapeutic level each day by mouth In addition, intramuscular injections of fat-soluble vitamins may be given prophylactically once a month at the following dosage level

Vitamin K — 10 mg	intramuscularly monthly
Vitamin A — 100,000 units	
Vitamin D — 100,000 units	

If prothrombin levels are low, vitamin K may have to be given by intramuscular injection each day until the deficiency is corrected Bone lesions, if present, may have to be treated vigorously with vitamin D 100,000 units a week A maintenance dose of 6 gm of calcium gluconate per day should be taken in addition to skim milk, buttermilk and other high calcium containing foods If there is severe osteomalacia, the calcium should be increased to 2–3 times the maintenance dose per day

There is some evidence that the anemia of chronic obstructive jaundice is the result of iron deficiency, and if there is no response to vitamin B-complex medication, ferrous sulphate grains, 7½ per day, may have to be continued indefinitely Occasionally intravenous iron therapy or trans fusions may be necessary

The development of *cirrhosis in chronic obstructive jaundice* needs special dietary attention This is indicated in the section on "Cirrhosis of the Liver"

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Chapter 23

Diet in the Treatment of Diabetes Mellitus

By HOWARD F ROOT AND C CABELL BAILEY

INTRODUCTION

DIABETES mellitus may be defined as an hereditary disorder of carbohydrate metabolism characterized by the presence of dextrose in the urine and persistent hyperglycemia Its major clinical features depend upon hypoinsulinism resulting from deficient production, reduced effectiveness, or increased destruction of insulin secreted by the islands of Langerhans The diabetic pattern, in the anthropologic sense,[1,2] is based upon the hereditary transmission of pancreatic inferiority, defined as insufficiency of the island cell reserve The inherited diabetic trait may involve more than one gene or multiple genes at varying ages of onset of diabetes Against this hereditary background, there develop various types of pancreatic pathology and of abnormal metabolic and endocrine behavior Thus, disturbances in the balance between the glucagon-producing alpha cells of the islets and the beta cells are now being studied (Ferner[6] Warren[3] and LeCompte[35]) Hereditary transmission of diabetic susceptibility as a Mendelian character explains the persistence of the pattern The permanence of this tendency may be checked by various factors, including sterility, impotence, failure to produce offspring, or, possibly, the phenomenon of anticipation observed in some diabetic families Since patients live many years longer today than formerly, certain aspects of the disease now present themselves which were not previously evident These include premature vascular disease disturbances in the endocrine system (exemplified by loss of potency in the male), toxemias of pregnancy, and susceptibility to infection and to various neuropathies The development of diabetes depends upon the transmission of a tendency to the disease which may pass unrecognized for a lifetime, or at least until infection, metabolic stress (hyperthyroidism, etc), or local injury, as in hemochromatosis or pancreatitis, bring it to the surface This conception of the pattern emphasizes the need for early and long-continued treatment of the individual patient, and also for prophylactic dietary and eugenic measures for his family The protection of the patient's pancreas becomes the central objective and the dietary regimen the cornerstone of treatment first, to spare the pancreatic insulin, second, to make the action of insulin most efficient, and finally, to insure satisfactory nutrition

FACTORS INFLUENCING THE PRODUCTION OF INSULIN OR THE AMELIORATION OF DIABETES

In the experimental diabetic state produced by alloxan, it is possible to study varying degrees of severity of the condition and the effects of agents in

improving the condition Lazarow[4] and others have studied the relationship between sulfhydryl compounds and the production of diabetes The metabolism of the beta cell is dependent on cysteine Insulin is 12 per cent cysteine Various nutritional factors seem in some way to affect the processes by which insulin may be formed Spontaneous recovery from diabetes in alloxanized animals may occur within a period of two years, according to Lazarow The relationship of the various factors which may influence the regeneration of beta cells is a subject demanding intensive study Born tein's investigations in adrenomedullated hypophysectomized animals indicated that the plasma of young diabetics contains little or no insulin and that even in adults the amount of insulin in the human plasma is greatly reduced This correlates well with the demonstration of Wrenshall *et al* [5] of the absence of insulin in the young diabetic patient s pancreas at autopsy and the finding of moderate amounts of insulin in the pancreas of middle aged diabetics A new and possibly more accurate method of assay of insulin or at least insulin like activity in the blood, introduced by Martin Renold and Dagenais,[6] may give new and broader concepts of the conditions affecting insulin production and release The studies of Renold[7] indicated that the normal fasting plasma level is in the neighborhood of 100 to 500 micro units of insulin per ml The remarkable fact is that the simultaneous injection of glutathione and cysteine protects animals from the diabetes produced by alloxan injection The studies of F M Allen upon partially depancreatized dogs indicated that diabetes with permanent change in the function of the islands of Langerhans resulted from long continued functional over train of these islands It was early shown that obesity is the most common condition predisposing to the development of diabetes in adults (though not in children) and particularly in adults with a family history of diabetes [8]

Newburgh[9] emphasized the remarkable improvement shown in cases of diabetes when obesity is controlled by proper diet A series of brilliant investigations followed F G Young s discovery of a crude extract of the anterior pituitary [10] a preparation which, when injected daily for a period of ten days would produce permanent diabetes with degenerative changes in the islands of Langerhans This discovery made possible the experimental production of both temporary and permanent diabetes and hence facilitated observation of the role of diet in protecting the islands of Langerhans against injury and in encouraging recovery from the disease One may mention here only a few of many articles by Best, Lukens, Long, Haist, Campbell, Ham and Houssay[10-17] and emphasize their conclusions

By Young s method of injection a gradual fall in the insulin content of the pancreas was made to occur in dogs together with a progressive change in the beta cells of the islands These effects are apparently due to a pro found extra pancreatic action of the extract as indicated by pathologic evidence of changes in the thyroid gland, adrenal cortex and liver The result is excessive strain of the islands of Langerhans and the production of diabetes This extraordinary fact was revealed however by Best s experi ments that if dogs were made to fast the pituitary extract lost its power of injuring the islands of Langerhans Indeed, if insulin was given with the extract the island cells were protected against injury

The effect of diet on insulin production has been strikingly shown In certain experiments, fasting and fat-feeding as well as the administration of insulin allowed the islets to rest and decreased the amount of insulin produced More important, Lukens and Dohan[18] succeeded in bringing about complete recovery of the island cells in the cat Return to normal structure and disappearance of diabetes could be achieved, it was found, if insulin and dietary treatment were used soon enough after the island cells had been injured by anterior pituitary extract These experiments have demonstrated that the island cells can be slightly injured, temporarily or permanently, that dietary means protect the island cells against injury, and that the combination of dietary treatment and insulin makes possible the complete cure of diabetes in early cases if treatment is carried out before permanent changes have taken place

The Prevention and Cure of Diabetes —The possibility of a cure has been discussed repeatedly Remissions of diabetes persisting for periods varying from three to seven years have been described The patients with long periods of remission were cases discovered early and treated vigorously with both diet and insulin [19]

If diabetes is to be attacked as a eugenic problem, it must be done by the development of a conviction in the community against the marriage of a diabetic to a diabetic, or into a diabetic family The first step in the prevention of diabetes should be the discovery of all cases of the disorder as early as possible With the discovery of a case of diabetes, all relatives of the patient should be informed of the existence of diabetes in the family in order that they may be advised of methods by which they may prevent the development of diabetes in themselves

Among other things, the following rules should be given the members of such a family First, avoid overweight keep the body weight 10 per cent below average after the age of thirty Second, exercise for muscular exercise will keep down body weight and help the body increase utilization of carbohydrates The efficiency of insulin action is always increased by muscular exercise, and a method of sparing pancreatic function is thus afforded

PRINCIPLES OF DIETARY THERAPY

In prescribing diets for diabetic patients, the individual need for the patient must be kept clearly in mind The mere stipulation of specified amounts of carbohydrate, protein and fat to attain the caloric value in accordance with standard tables may fail entirely to provide a satisfactory diet for the patient s needs at the time One may classify diabetic patients as seen in the hospital or office under three headings with respect to diet

A Uncontrolled or "decompensated' diabetes, as illustrated by the patient with diabetes recently discovered or by the patient of long duration who presents hyperglycemia and marked glycosuria Such patients may be rapidly improved with a return of hyperglycemia to normal levels with the aid of a diet with caloric levels, during the hospital stay, reduced to that of the calculated basal metabolism If, with this restricted diet insulin is employed, rapid reduction of glycosuria and hyperglycemia may occur, and within a comparatively short period with improving tolerance

the diet may be increased to a level commensurate with their needs after hospital discharge and upon return to normal activity This reduction in total calories is of particular value and importance in the treatment of children or young adults early in the course of the disease in whom a remission of diabetes may be anticipated

B Emergency situations, such as diabetic ketosis, uremia, hemorrhage from peptic ulcer, and particularly post-surgical periods

C Diabetic diets for long-continued use, after recovery from emergencies and from decompensation, may be planned in accordance with the following principles

(1) The total calories must be sufficient for the age, sex activity, and growth requirements of the patient Ordinarily most diets vary between 1600 and 2400 calories with diets ranging from 2500 to 3500 calories allowed for individuals with strenuous activities

(2) The total calories and the proportions of carbohydrate, protein and fat at each meal remain approximately the same from day to day, although the specific foods consumed vary greatly

(3) The carbohydrate content of the diet is usually less than the normal diet—primarily the result of the elimination of concentrated sweets and pastries The protein and fat content seems to be a little higher than the usual home diet, to make up for a deficiency of calories from concentrated carbohydrate

The carbohydrate prescribed should very rarely exceed 225 grams, and usually does not exceed 200 grams

(4) The calories prescribed should be estimated for the patient s ideal rather than actual, weight In this way, an obese patient will lose weight and an undernourished one gain

(5) The diet must contain adequate vitamins and minerals

(6) Such a diet should be prescribed as will be most completely and normally utilized through the action of endogenous and administered insulin

COMPOSITION OF THE DIABETIC DIET

One third of the carbohydrate content of the average diabetic diet is supplied by bread (50 gm), one third by fruit (50 gm) and one-third by vegetables milk and cream and cereal This division simplifies the handling of a diabetic diet and is particularly helpful in the teaching of dietary therapy to patients and students

The diet of the diabetic patient should be superior to the ordinary diet, for the necessary constancy from day to day does not allow for making up the errors of one day on the next The food embraced by such a diet should be the best food and should supply mineral salts and vitamins in generous amounts

Calories – The caloric needs of the diabetic are the same as those of a normal individual Within broad limits, carbohydrate protein and fat are interchangeable so far as energy production is concerned However, Peters[20] has well described the important distinction between the energy-producing function of these substances and their transformative functions

Thus the transformative functions of protein cannot be supplied by carbohydrate or fat, since neither contains nitrogen, sulfur, or the complex radicals found in protein. In recent years, there has been a tendency to minimize the importance of calories. Nevertheless, the calorie is as important to the diabetic as ever.*

If the body is not to consume its own tissues for fuel, the caloric value of the ingested foods for each twenty-four hours must be equal to the energy required by the body for that period. The calorie needs, then, may be considered to consist of the basal metabolic need plus an allowance for work. This work allowance will vary with the type of activity. Thus the adult allowance for sedentary work may be between 500 and 600 calories, for light work, between 800 and 1200 calories, for moderate work, between 1200 and 1500 calories, and for heavy laborious work, between 1500 and 4000 calories.[0]

TABLE 82.—DIET IS FUNDAMENTAL IN DIABETIC THERAPY
A Basic Introductory Diabetic Diet Is Simple

Food	*Unit portion*	*Example Grams in Each Portion* *Weight*	*C*	*P*	*F*	*Total daily portions*	*Total Grams* *C*	*P*	*F*
Bread	1 slice	30	15	2.5		3	54	9	
Oatmeal	1 large	30, dry	20	5	2	1	20	5	2
Orange	1	150	15			3	45		
Vegetables 3-5%	1 cup	150	5	2.5		4	20	10	
Milk	¼ pt	120	6	4	4	1	6	4	4
Cream 20%	¼ pt	120	4	4	24	1	4	4	24
Egg	1	60		6	6	1		6	5
Meat	1 small	60		16	10	2		32	20
Butter	1 square	10			8	3			25

Grand total grams (approximate)	C150	P70	F80
Calories per gram	× 4	× 4	× 9
Total calories — 1600 =	600 +	280 +	720

This Can Be Modified as Necessary

Sample card given to diabetic patients

Children need more food per kilogram of body weight than adults. It is a good rule to prescribe 1000 daily calories for a child one year old and to add 100 daily calories to his diet for each year of his age until he has completed growth. Since epiphyseal closure in girls occurs at the menarche, our rule at the Deaconess Hospital has been to prescribe no more than 2200 calories for girls. For boys, however, a maximum of 2800 calories at nineteen years of age is to be prescribed.

The best way to help the patient, secure his cooperation, and understand the problem of diabetic nutrition is to prescribe the diet in grams and to

* Hardly a week passes when it is not possible to demonstrate to the diabetic class of patients at the Deaconess Hospital the record of a patient in whose twenty-four hour urinary excretion 8 to 10 per cent of glucose or an equivalent of 1 pound of sugar was lost. When patients see that the calories lost in two such days of uncontrolled diabetes provide sufficient calories for the maintenance of a soldier for one day, they begin to understand the meaning of carbohydrate balance.

use scales Time and again the mother of a diabetic child has expressed great relief at having a diet prescribed definitely by weight She finds relief from this worry when the uncertainty involved in trying to follow general directions is replaced by consciousness that she is following exact rules given her Nevertheless, many patients with mild diabetes and some patients with diabetes of moderate severity can learn to measure their food by means of household measures with great accuracy This is more apt to occur with patients who actually weigh their food for the first few months of treatment

Proportions of Foodstuffs —The proportion of carbohydrate, protein, and fat is ordinarily in the neighborhood of 2 gm carbohydrate to 1 of fat and 1 of protein The total carbohydrate prescribed in most adult diabetic diets varies from 130 to 200 gm

Formerly, diabetic diets contained an excessive amount of protein, from 100 to 150 gm a day Best and Taylor, quoting the work of Chittenden,[21] state that nitrogen equilibrium can be accomplished with as little as 25 gm of class A protein An amount varying from 0 6 to 0 7 gm per kg of body weight was at one time favored However it has been pointed out that, even though adaptation is possible which would bring about nitrogen equilibrium by means of low levels, this is by no means an optimal arrangement A protein diet from 70 to 100 gm is at present preferable

Since fat can come from carbohydrate, one might argue against its being essential in the diet However, leaving aside the fat soluble vitamins, fat is necessary Fat-free diets prevent growth Linoleic and linolenic acids are necessary to prevent arrested growth and dermatitis in experimental animals Fat is an excellent source of calories Its efficiency as fuel for muscular work is only 10 to 12 per cent less than that of carbohydrate (Krogh and Lindhard)

TABLE 83 —THE CARBOHYDRATE CONTENT OF VEGETABLES FRESH OR CANNED

	3 Per cent	*6 Per cent*	*20 Per cent*
Lettuce	Tomatoes	String beans	Potatoes
Cucumbers	Water cress	Brussels sprouts	Shell beans
Spinach	Sea kale	Pumpkin	Baked beans
Asparagus	Cauliflower	Turnip	Lima beans
Rhubarb	Egg plant	Squash	Green corn
Endive	Cabbage	Okra	Boiled rice
Marrow	Radishes	Beets	Boiled macaroni
Sorrell	Leeks	Carrots	
Sauerkraut	Str beans young	Onions	
Beet greens	Broccoli	Green peas	
Dandelions	French artichokes		
Swiss chard	Green peppers		
Celery	Summer squash		
Mushrooms	Kohl rabi		

Carbohydrate Foods —*Vegetables* —These vary greatly in their carbohydrate value, from lettuce, which contains 2 2 per cent to potatoes and beans which contain 20 per cent or more carbohydrate For the convenience of the diabetic patient, and without any great sacrifice of accuracy, these

may be classified as 3, 6, and 20 per cent vegetables (see Table 83) The average amount of carbohydrate in the 5 per cent group nevertheless is actually about 3 per cent, hence 150 gm (1 saucer) of vegetables in this group are calculated to give only 5 gm of carbohydrate The 10 per cent group likewise average 6 per cent carbohydrate, therefore, 150 gm (1 saucer) are estimated as 10 gm of carbohydrate The 15 per cent and 20 per cent group, on the other hand, are considered to yield respectively, 15 and 20 gm of carbohydrate for each 100 gm of vegetable

By prescribing the 5 per cent vegetables especially, one can increase the bulk of the meal and satisfy the patient without greatly increasing the carbohydrate content of the diet If, on the other hand, the patient needs the calories in his diet but objects to the large quantity of food, one can concentrate the diet by prescribing more of the 15 per cent or 20 per cent vegetables and less or not any of the 5 per cent vegetables Besides adding bulk to the diet, the vegetables are important sources of vitamin A and essential minerals

TABLE 84 —APPROXIMATE CARBOHYDRATE SUBSTITUTION VALUES OF FRUITS FRESH OR CANNED (WATER PACKED)

Food	Carbohydrate *10 gm*	Carbohydrate *15 gm*
Grapefruit pulp	150	225
Strawberries	150	225
Watermelon	150	225
Cantaloupe	150	225
Blackberries	120	180
Orange pulp	100	150
Pears	90	135
Peaches	90	135
Apricots	80	120
Raspberries	80	120
Plums	80	120
Pineapple	70	105
Apple	70	105
Honeydew melon	70	105
Blueberries	70	105
Cherries	60	90
Banana	50	75
Prunes (cooked)	50	75
Ice cream	50	75

Fruit —Although diabetic diets call for one orange at each meal, that does not mean that the patient may eat only oranges as his fruit Table 84 gives a list of other fruits which the patient may substitute for oranges If, for instance, the patient wishes strawberries instead of his orange he may have them Ice cream is included with the fruits, since it may be substituted for an orange once or twice a week, 50 gm of ice cream = 100 gm of orange Obviously, this does not allow for the small amount of protein and fat in ice cream, but since it is not taken often, this can be ignored safely All kinds of ice cream are allowed, except French ice creams or ice

cream with whole nuts in it Fruits, which provide vitamin C, are used by diabetics in salads and desserts

Bread —White, whole wheat, rye, corn and brown bread are used interchangeably in the diabetic diet Gluten bread is not used, since whereas its carbohydrate content is much lower than that of other breads, it is 25 per cent protein When one recalls that 58 per cent of protein changes into carbohydrate in the body, the fallacy of the claimed value of this bread in treating diabetes is obvious Bread should be weighed before it is toasted if toast is desired Six saltines, or three Uneeda biscuits, or graham crackers may at times be substituted for one slice of bread Thiamin chloride and iron are found in moderate quantities in most breads Today bread enriched with vitamin B_1 is a very significant source of thiamin chloride It is worth recalling that whole-wheat bread contains from four to six times the amount of thiamin found in white bread Since bread is a concentrated source of carbohydrate, it is seldom advisable to prescribe more than one slice at each meal

Cereals —Oatmeal which is two-thirds carbohydrate, is usually given for the diabetic breakfast in dry-weight quantities of 15 gm This amounts to about half a bowl and after cooking, weighs about 120 gm —the difference being water In large diets even 30 gm of oatmeal may be given Patients often substitute in place of oatmeal other hot cereals such as farina or dry cereal such as corn flakes These substitutes will be discussed later Variety helps make the diet palatable and encourages the diabetic to follow his diet Most cereals contain thiamin and iron in moderate amounts and riboflavin and such minerals as phosphorus in smaller amounts

Milk —Though milk is not entirely carbohydrate it is considered under this heading for it contains $1\frac{1}{2}$ gm of carbohydrate, 1 gm of protein, and 1 gm of fat in each ounce Milk, a balanced food, contains all the vitamins in small amounts It is an important source of calcium

Protein Foods —The protein in the diabetic diet is obtained primarily from meat, fish fowl, eggs bacon, and cheese Small amounts are secured from milk cream cereals, bread, and even vegetables

The quantity of protein desirable in the diet varies from 3 gm per kilogram of body weight in the child to approximately 1 gm per kilogram in the adult Beef, lamb and pork vary so little in their food value that the lean meat of each is considered for convenience to contain per ounce 7 gm of protein and 5 gm of fat but no carbohydrate at all Although beef liver and veal liver contain approximately 3 gm of carbohydrate per 100 gm, this amount is negligible

Fat free fish differ from meat in having little or no fat and are calculated to contain per ounce an average of 6 gm of protein but no carbohydrate or fat Fat fish averages about the same for protein and fat as meat

Eggs are regularly prescribed and add vitamins A, B and D as well as minerals, among them sulfur to the diet

Gelatin though it contains 84 per cent protein, does not contain the important amino acids, tryptophan and cysteine and is therefore not so satisfactory a protein as meat Furthermore gelatin is poor in vitamins

In treating diabetics, one must bear in mind that 58 per cent of the protein ingested changes into carbohydrate in the body

Fats —The principal sources of fat in the diet of a diabetic are butter, cream, bacon, eggs, cheese, and meat Table 85 reveals the relative amount of fat in each Before the days of insulin, fat formed the bulk of the diabetic diet, but today slightly less than one-half the calories are obtained from fat The non-diabetic secures approximately one-third of his calories from fat

TABLE 85 —FOOD VALUES IN THE DIABETIC DIET*

30 Grams 1 oz contain approximately	*Carbohydrate gm*	*Protein gm*	*Fat, gm*	*Calories*
Vegetables 5%	1	0 5	0	6
Vegetables 10%	2	0 5	0	10
Oatmeal dry weight	20	5	2	118
Shredded wheat, 1	23	3	0	104
Potato	6	1	0	28
Bread	15	2 5	0	84
Uneeda biscuits, 2	10	1	1	53
Milk	1 5	1	1	19
Egg one	0	6	6	78
Meat, cooked, lean	0	7	5	77
Fish fat-free	0	6	0	24
Chicken, cooked lean	0	8	3	59
Oysters 6	4	6	1	49
Cheese	0	8	11	131
Bacon	0	5	15	155
Cream 20%	1	1	6	62
Cream 40%	1	1	12	116
Butter	0	0	25	225
Oil	0	0	30	270

* 1 gm carbohydrate 4 calories
1 gm protein 4 calories
1 gm fat, 9 calories
6 25 gm protein contain 1 gm nitrogen
A patient at rest requires 25 calories per kilogram
Water clear broths coffee tea cocoa shells and cracked cocoa can be taken without allowance for food content

Acidosis is precipitated by a diet containing so high an amount of fat that it can not normally be utilized It has been shown that fat dogs are more susceptible to acidosis than thin dogs The high fat diet, furthermore, is unpalatable to most people and it has been shown that tolerance for carbohydrate is less when the patient is taking a low-carbohydrate but high-fat diet

Whether or not a high-fat high cholesterol diet hastens arteriosclerosis, the most dreaded enemy of the diabetic will require still further study Certainly such diets in the presence of insufficiently controlled diabetes lead to hyperlipemia A vast literature, both experimental and clinical, at present strongly suggests that diets high in saturated fatty acids may play an important part in producing atherosclerosis A recent review of studies bearing upon the relationship of such a diet to the premature cardio-

renal vascular disease of diabetes is given by Joslin, Root, White and Marble[1] The use of diets providing fat from vegetable sources and therefore containing unsaturated fatty acid is becoming more frequent

With the general use of insulin and correspondingly larger amounts of carbohydrate in the diet the significance of the ketogenic antiketogenic ratio has disappeared Stadie's work was the culmination of a long series of studies by many workers He emphasized that the ketone bodies, which formerly were considered toxic and unavailable for use in the body, are the normal end products of fatty acid oxidation in the liver and that they are utilized in the peripheral tissues by both normal and diabetic subjects It is only when the ketone bodies accumulate, owing to the excessively rapid breakdown of the fatty acid molecule—as in diabetic acidosis, when insulin is inadequate—that the ketone bodies are produced more rapidly than they can be utilized They then have a toxic effect because their acidic properties disturb acid base equilibrium electrolyte balance, and water exchange He further showed that the earlier premise of "obligatory coupling of the ketones and carbohydrate oxidation was a false one He supported Hurtley's theory of multiple alternate oxidation of the fatty acid chain, and not Knoop's concept of successive beta oxidation Finally, his work as well as others gave no support to the idea that fatty acids are converted into glucose in the liver

When the low-carbohydrate high-fat diet is used insufficient calories are obtained from the carbohydrates and hence excess fatty acid breakdown is necessary to meet caloric requirements In this way, this diet causes the formation of excess ketone bodies and favors acidosis The usual diabetic diet today contains from 75 to 125 gm of fat the majority of such diets containing between 80 and 100 gm in a twenty four-hour period

Approximate Equivalents —Substituting one food for another in the diabetic diet has always been an important means of making the diet more palatable, variable and convenient Table 86 is the outline of instructions given patients at the New England Deaconess Hospital to facilitate substitutions with foods that are approximately equivalent in carbohydrate, protein and fat content

For 1 ounce of meat or 15 gm (2 strips) of bacon the diabetic may substitute 1 egg 15 gm of peanut butter, or 30 gm of any cheese, except creamed or cottage cheese of which he is allowed 30 gm or 5 oysters clams, shrimps or scallops plus 5 gm butter

Butter may be replaced with an equal quantity of oleomargarine or mayonnaise Parents of Italian descent especially find an equal quantity of olive oil a welcome substitute for butter If necessary, even cream or bacon may occasionally be substituted

For 15 gm of oatmeal one may substitute 13 gm (dry weight) of another hot cereal such as Farina or Cream of Wheat or 12 gm of dry cereals such as corn flakes or Rice Krispies Other substitutions for oatmeal are half a Shredded Wheat Biscuit half a slice of bread (15 gm) or 100 gm of orange With these substitutes a diabetic can have a variable and satisfactory breakfast

Substitutions for bread fruit milk vegetables and a few selected foods are found in Table 86 and are self-explanatory

In treating diabetics, one must bear in mind that 58 per cent of the protein ingested changes into carbohydrate in the body

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Vegetables, 10%	2	0 5	0	10
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Shredded wheat, 1	23	3	0	104
Potato	6	1	0	28
Bread	15	2 5	0	84
Uneeda biscuits, 2	10	1	1	53
Milk	1 5	1	1	19
Egg one	0	6	6	78
Meat, cooked lean	0	7	5	77
Fish fat-free	0	6	0	24
Chicken, cooked, lean	0	8	3	59
Oysters 6	4	6	1	49
Cheese	0	8	11	131
Bacon	0	5	15	155
Cream, 20%	1	1	6	62
Cream 40%	1	1	12	116
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Oil	0	0	30	270

* 1 gm carbohydrate 4 calories
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1 gm fat 9 calories
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When the low-carbohydrate, high fat diet is used, insufficient calories are obtained from the carbohydrates and hence excess fatty acid breakdown is necessary to meet caloric requirements. In this way this diet causes the formation of excess ketone bodies and favors acidosis. The usual diabetic diet today contains from 75 to 125 gm. of fat, the majority of such diets containing between 80 and 100 gm. in a twenty-four-hour period.

Approximate Equivalents.—Substituting one food for another in the diabetic diet has always been an important means of making the diet more palatable, variable and convenient. Table 86 is the outline of instructions given patients at the New England Deaconess Hospital to facilitate substitutions with foods that are approximately equivalent in carbohydrate, protein and fat content.

For 1 ounce of meat or 15 gm. (2 strips) of bacon, the diabetic may substitute 1 egg, 15 gm. of peanut butter, or 30 gm. of any cheese except creamed or cottage cheese, of which he is allowed 30 gm., or 5 oysters, clams, shrimps or scallops plus 5 gm. butter.

Butter may be replaced with an equal quantity of oleomargarine or mayonnaise. Patients of Italian descent, especially, find an equal quantity of olive oil a welcome substitute for butter. If necessary, even cream or bacon may occasionally be substituted.

For 15 gm. of oatmeal one may substitute 13 gm. (dry weight) of another hot cereal, such as Farina or Cream of Wheat, or 12 gm. of dry cereals such as corn flakes or Rice Krispie. Other substitutions for oatmeal are half a Shredded Wheat Biscuit, half a slice of bread (15 gm.), or 100 gm. of orange. With these substitutes, a diabetic can have a variable and satisfactory breakfast.

Substitutions for bread, fruit, milk, vegetables and a few selected foods are found in Table 86 and are self-explanatory.

Sick Day Diet.—Usually, when the diabetic develops a severe cold or a mild attack of grippe, a soft diet containing the following ingredients will be found to give sufficient nourishment: three slices of bread (90 gm.), which may be toasted, half a bowl of oatmeal (15 gm.), 3 small pats of butter (15 gm.), 1 egg, 3 oranges (450 gm.), and a quart of milk. If this is divided into three meals, it will give a soft diet containing carbohydrate 157 gm., proteins 50 gm., and fats 50 gm.

If the patient is ill and can tolerate only a liquid diet, such a diet might consist of one quart of milk, one pint of orange juice, one pint of ginger ale. If they are not sick enough for hospitalization, the patients can easily prepare these sick day diets in their home.

Substitutions for School or Picnic Lunches.—Fortunately for the diabetic child, many schools today have cafeterias where vegetables, meat, and other articles of the diabetic diet are available. The majority of schools, however, sell only sandwiches to the children or no food at all. For this reason, a great many diabetic pupils must take their lunches to school.

In sandwiches a large spreading surface is desirable, most diabetic diets, however, offer only one slice of bread for lunch. If, however, we use the approximate equivalent table, we find that 1 slice of bread (30 gm.) may replace 150 gm. of 10 per cent vegetables plus 150 gm. of 5 per cent vegetables. With 60 gm. of bread, if the crust is removed and the bread sliced thin, there will be 4 thin slices, enough for 2 sandwiches.

The filling of the sandwich should be equivalent to 30 gm. of meat, or one-half the amount usually prescribed for dinner. The diabetic child may therefore have a cheese sandwich, an egg and lettuce sandwich, a meat or fowl sandwich, a peanut butter sandwich, or a cottage cheese sandwich. Since two very thin slices of tomato and lettuce have practically no food value, a tomato, bacon, and lettuce sandwich is allowable. The child may prefer to use mayonnaise on his bread instead of butter. His fruit allowance will provide him with a good dessert, but, if he likes, once a week he may substitute 50 gm. of ice cream (a small scoop) for 100 gm. of orange. Fifty grams of ice cream in a cone may occasionally replace 150 gm. of orange. Milk for the diabetic child's diet is usually available at the school cafeteria or a nearby drugstore in half-pint bottles.

TABLE 86.—JOSLIN CLINIC

FOOD EXCHANGES

Most foods consists of carbohydrate, protein, and/or fat, varying combinations. One food may be exchanged for another only if their food value is similar.

Carbohydrates: for energy		*Proteins*: to build muscles and tissues	*Fat*: for energy and weight
Sugar	Starch	Lean meats	Butter
Fruits	Vegetables	Fish—Fowl	Cream
Bread	Rice	Egg	Cream Cheese
Cereal	Milk	Cheese	Bacon
Macaroni	Flour	Cottage Cheese	Oil

HOUSEHOLD MEASUREMENTS

30 grams = 1 ounce	1 cup = 240 grams = 8 ounces
5 grams = 1 teaspoon	¾ cup = 180 grams = 6 ounces
3 tsps = 1 tblsp	½ cup = 120 grams = 4 ounces
2 tblsp = grams 1 ounce	¼ cup = 60 grams = 2 ounces

APPROXIMATE SUBSTITUTES FOR FOODS ON DIET SHEET

Substitutes for 1 ounce (30 grams) of lean meat (any kind)

1 egg
2 full sized strips bacon (15 grams)
1 ounce fish or fowl (30 grams)
5 oysters clams shrimps scallops (all small) plus 1 teasp butter
1 ounce or 1 slice American cheese (30 grams) omit 1 teasp butter
1 ounce creamed cottage cheese (30 grams)
1 tablespoon peanutbutter (15 grams)
2 ounces meat = 1 pound live chicken lobster plus 2 teasp butter

Substitutes for two Uneedas (food value of following = 10 gms carbohydrate)

2 graham crackers
2 double squares Ry Krisp (13 gms)
3 Arrow Root biscuits
4 saltines
5 Ritz (also Cheese Ritz)
3 Ginger snaps
3 Butter Thins
8 Wheat Thins
3 Chocolate Snaps (8 1 gms)
15 oyster crackers
⅔ slice bread (20 gm)
½ cup cooked cereal (oatmeal) (—120 gms)
12 gms dry prepared cereal (cornflakes etc) (—¾ cup)
100 gms orange (small)
5 small Vanilla wafers
1 cup popped corn (15 gms)

Substitutes for 1 slice bread (30 gms) (following foods = 15 gms carbohydrate)

2½ ounces (medium) potato (75 gms)—½ cup whipped
Add 20 gms to baked potato to allow for skin
⅓ cup corn lima beans shell beans (75 gms)
⅔ cup parsnips
½ cup cooked rice (75 gms)
½ cup cooked macaroni spaghetti noodles (75 gms)
1 medium bran muffin without raisins (30 gms)
1 slice pumpernickle (30 gms)
1 Pilot cracker
1 Matzoth (20 gms)
Medium orange (150 gms)
1 small corn muffin (30 gms)
½ English Muffin (30 gms)

Always use regular bread dark or white *Do not use* Protein or Gluten breads (Diet Breads)

Substitutes for 1 teaspoon butter (5 gms) (following foods = 4 gms fat)

1 teaspoon margarine
1 teaspoon mayonnaise
1 teaspoon salad oil
1 teaspoon peanutbutter
1 tablespoon French Dressing
1 tablespoon light cream (15 gms)
2 teaspoons cream cheese
1 slice bacon

For 2 teaspoons butter 1 tablespoon sour cream
1 tablespoon heavy cream
1 heaping tablespoon whipped cream (with Sucaryl)

FRUIT SUBSTITUTIONS

All fruits fresh or Dietetic water packed All fruit juices unsweetened All fruits cooked without sugar Weight of fruit equal to the weight of the fruit juice

IN PLACE OF 100 GMS OF ORANGE (SMALL)

⅔ medium grapefruit (150 gms)
1 cup strawberries (150 gms)
¾ cup watermelon (150 gms)
½ cantaloupe (150 gms)
⅔ cup blackberries (120 gms)
1 small pear (90 gms)
½ cup fruit cocktail (90 gms)
1 medium peach (90 gms)
½ cup raspberries (80 gms)
2 medium plums (80 gms)
¼ cup stewed aprictos (80 gms)
⅓ medium Papaya (100 gms)
½ cup blue berries (70 gms)
¼ cup pineapple (70 gms)
¼ cup applesauce (80 gms)
⅛ honeydew melon (70 gms)
½ small Mango (55 gms)
9 cherries (60 gms)
⅓ small banana (50 gms)
3 prunes without sugar (50 gms)
¾ serving Jello (50 gms) Regular
Ice Cream (50 gms) plain flavors—
once a week
1 cup Tomato juice (240 gms)
1 large Tangerine

IN PLACE OF 150 GMS OF ORANGE (MEDIUM)

1 medium grapefruit (225 gms)
1½ cups strawberries (225 gms)
1 cup watermelon (225 gms)
¾ cantaloupe (225 gms)
¾ cup blackberries (180 gms)
½ medium Papaya (150 gms)
1 medium pear (135 gms)
1½ medium peach (135 gms)
¾ cup fruit cocktail (135 gms)
¾ cup raspberries (120 gms)
3 medium plums (120 gms)
½ cup stewed or 2 ripe aprictos (120 gms)
¾ cup blueberries (105 gms)
½ cup or 2 slices pineapple (105 gms)
½ cup applesauce without sugar (120 gms)
1 small apple (105 gms)
¼ honeydewmelon (105 gms)
13 cherries (90 gms)
50 average green seedless grapes (90 gms)
¾ small Mango (80 gms)
¾ banana (75 gms)
5 stewed prunes without sugar (75 gms)
1 serving Jello (75 gms) Regular
1 small serving Ice Cream
plain flavors—once a week (75 gms)

ADDITIONAL SUBSTITUTIONS

1 Canned Soups *Avoid Bean and Bacon Soups*

⅓ can soup plus water (100 gms soup plus water) — 150 gms 3 per cent plus 75 gms 6 per cent veg at one meal Or 20 gms (⅔ slice) bread Exchange remaining ⅓ slice bread for 1 uneeda if desired

2 Creamed Soups or Chowders
⅓ can concentrate soup plus ½ cup milk = 1 slice bread plus 1 ounce meat
3 Baked Custard (made with Sucaryl) 120 gms = 100 gms orange plus 1 ounce meat
4 Sponge Cake (plain) 30 gms = 1 slice bread—use occasionally—or 150 gms orange
5 Beans and Pork (canned) ½ cup (130 gms) = 1 slice bread plus 2 vegetables at one meal plus 2 teaspoons butter
6 Donut (plain) 30 gms (small) = 1 slice bread plus 2 teaspoons butter
7 Potato Chips (30 gms —10 cent bag) = 1 slice bread plus 2 teaspoons butter

3 P M Lunch—1½ uneedas plus ½ cup milk =

1 ¾ cup dry prepared cereal plus ½ cup milk
2 3 Uneedas plus 1 tablespoon peanutbutter (no milk)
3 3 Uneedas plus ½ ounce (15 gms) American Cheese (no milk)
4 2 Uneedas plus 1 teaspoon butter plus ½ cup skim milk
5 1 package peanutbutter NABS (4 sandwiches) (no milk)

FOODS WITH LITTLE OR NO FOOD VALUE

Black tea or coffee
Bouillon (canned or cubed)
Consomme and clear broths
Sour and dill pickles
3 per cent vegetables
Condiments
Unflavored gelatins (D Zerta)
Cranberries (without sugar)
Rhubarb (without sugar)
Mustard
Ketchup
Horseradish
White vinegar (avoid cider)
Sugar free beverages
Raw onion
Lemon
Dietetic hard candy
Dietetic salad dressings (See Joslin Manual)
Dietetic maple syrup
Dietetic chewing gum

FOODS TO BE AVOIDED (unless by physician s order)

Sugar
Alcoholic Beverages
Cake—Pies—Desserts etc
Condensed Milk
Soft Drinks (Regular)
Special Dietetic Foods
Jellies and Marmalade
Raisins—Postum
Deep Fried Foods
Mollasses—Honey, Syrups

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DIABETIC DIETS

Standard Diabetic Diets —An average diet for a diabetic leaving the New England Deaconess Hospital is calculated for a patient weighing 130 lbs and engaged in relatively light work It consists approximately, of 165 gm of carbohydrate, 82 gm of protein and 97 gm of fat—or 1 861 calories This diet is shown in Table 87

TABLE 87 —STANDARD DIABETIC DIET FOR PATIENT WEIGHING 130 POUNDS

	Breakfast		*Dinner*		*Supper*	
Foods	*gm*	*Portions*	*gm*	*Portions*	*gm*	*Portions*
Eggs		1				
Meat lean cooked			75	Medium serving	75	Medium serving
Bacon	15	2 strips				
5% vegetables			150	1 saucer	150	1 saucer
10% vegetables						
Oatmeal dry						
Oatmeal cooked	15	⅓ bowl				
Uneeda crackers						
Butter	10	1 square	10	1 square	10	1 square
Cream 20%	60	2 ounces	30	1 ounce	30	1 ounce
Milk	120 cc	½ glass			120 cc	½ glass
Orange	150	1 medium	150	1 medium	150	1 medium
Cheese						
Potato Irish			75	1 medium	75	1 medium
Bread whole wheat	30	1 slice	30	1 slice	30	1 slice

If protamine zinc insulin is given the supper is light and two Uneeda crackers are given at bedtime To allow for the crackers, the potato for dinner and supper is reduced to 60 gm at each meal

TABLE 88 —DIABETIC DIETS

Diets	Total Diet				Carbohydrate (C)						Protein and Fat (PF)				
	Carbohydrate	*Protein*	*Fat*	*Calories*	*5% Vegetables*	*Orange*	*Oatmeal*	*Potato*	*Bread*	*Milk*	*Egg*	*Meat*	*Bacon*	*20% Cream*	*Butter*
C1 PF1	121	53	64	1272	300	400	15	90	45	240	1	75		120	15
C2 PF2	136	60	71	1423	300	400	15	120	60	240	1	90		120	20
C3 PF3	151	70	80	1604	300	400	15	150	75	240	1	120		120	25
C4 PF4	165	82	97	1861	300	450	15	150	90	240	1	150	15	120	30
C5 PF5	180	89	103	2003	300	450	15	180	105	240	1	165	15	120	35
C6 PF6	199	99	123	2299	300	450	30	180	120	240	1	180	30	120	45
Acute Illness	152	50	52	1276		400	15		90	960	1				15

Approximate equivalents 1 small orange (100 gm) = ½ banana (50 gm) = ½ saucer oatmeal (15 gm dry or 120 gm cooked) = 2 large saucers (300 gm) 5% vegetables = 1 large saucer (150 gm) 10% vegetables = potato size of egg = ½ slice (15 gm) bread

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If NPH insulin is prescribed a mid afternoon lunch such as ½ cup (120 gm) milk and 2 Uneeda crackers are given in addition to the small bedtime lunch

Table 85 shows the amount of carbohydrate protein, and fat in the basic foods These figures are given for 30 gm (1 ounce) since the amounts given in these diets are usually multiples of 30 gm

Table 88 is a list of diets developed at the Joslin Clinic intended for emergency use This list is printed on a card which the physician may carry in his vest pocket Such a list often proves convenient in giving instruction for patients or their families when far from the hospital or office as a temporary measure until permanent plans for treatment can be made The reason for the uneven numbers as carbohydrate, 165 gm, protein, 82 gm fat, 97 gm rather than carbohydrate, 160 gm, protein, 80 gm fat 90 gm—is to allow for full servings of the foods listed

THE EXCHANGE SYSTEM OF MEASURING

In an effort to standardize diabetic diets throughout the country, a joint committee of the American Diabetes Association, American Dietetic Association, and the Diabetes Section United States Public Health Service in 1950 described a simplified method for calculating diabetic diets

The committee divided all foods into six groups according to composition as designated in Table 89

TABLE 89 —COMPOSITION OF FOOD GROUPS

Food	*Approx measure 1 exchange*	*Weight gm*	*C gm*	*P gm*	*F gm*	*Calories*
Milk	1 cup (standard)	240	12	8	10	170
Vegetables	½ cup	100	7	2		36
Fruit	Exchange varies	Exchange varies	10			40
Bread exchanges	1 slice bread Other items vary	25 varies	15	2		68
Meat exchanges	1 ounce varies	30 varies		7	5	73
Fat exchanges	1 level tsp fat Other items vary	5 varies			5	45

To determine the basal caloric requirement using this method multiply the ideal weight in pounds by 10 Then add 100 to 200 calories if the patient is a young tall male Likewise subtract 100 to 200 calories if the patient is an elderly short female

For activity one adds 30 to 50 per cent to the basal calories Once the caloric requirements are determined, one can choose a sample A D A diet, as shown in Table 90

TABLE 90 —COMPOSITION OF A D A SAMPLE DIETS

	Carbohydrate gm	*Protein gm*	*Fat gm*	*Calories*
For adults				
1	125	60	50	1200
2	150	70	70	1500
3	180	80	80	1800
4	220	90	100	2200
For juveniles				
5	180	80	80	1800
6	250	100	130	2600

Table 91 illustrates the simplicity of this method To determine the amount of carbohydrate to be derived from bread, and thus the number of servings required, one adds the carbohydrate in the milk, vegetables, and fruit and subtracts this amount from the total carbohydrate in the diet One then determines the meat exchange by adding the protein in the milk, vegetables, and bread exchanges and deducting this figure from the total protein prescribed in the diet Finally, the amount of fat obtained from butter is determined by adding the fat in milk and meat and subtracting this from the total fat in the diet prescription

TABLE 91 —SIMPLIFIED PROCEDURE FOR CALCULATING A DIABETIC DIET

Prescription

Carbohydrate	— 180 gm
Protein	— 80 gm
Fat	— 70 gm
Calories	— 1700 gm

		Amount	*C*	*P*	*F*
Milk whole	(List I)	1 pint	24	16	20
Vegetables	(List II A)	As desired			
Vegetables	(List II B)	1 serving	7	2	
Fruit	(List III)	3 servings	30		
			61		
Bread exchanges	(List IV)	8 servings	120	16	
				34	
Meat exchanges	(List V)	7 servings		49	35
					55
Fat exchanges	(List VI)	3 servings			15
			181	83	70

By using the six exchange lists, one may make the diet varied and palatable List I includes the substitutes one may use for regular milk

LIST I—MILK

Carbohydrate 12 gm protein 8 gm, fat 10 gm per serving

Food	Approximate measure 1 exchange	Weight gm
Milk*	1 cup (8 oz)	240
Milk evaporated	½ cup	120
Milk powder, whole	¼ cup (3 tbsp level)	35
Buttermilk*	1 cup	240
Milk, skim*	1 cup	240

In List II, the vegetable exchanges are divided into A *Vegetables* and B *Vegetables* These are equivalent to 3 and 6 per cent vegetables, respectively as described earlier in this chapter

LIST II —VEGETABLES

A *Vegetables* —Negligible carbohydrate protein and fat in amounts ordinarily used

If more than one cup in cooked form is used at one meal it should be calculated as one serving of a Group B vegetable

Asparagus	Mushrooms	Watercress
Broccoli	Okra	Greens
Brussels sprouts	Parsley	Beet greens
Cabbage	Pepper green	Chard
Cauliflower	Radish	Collards
Celery	Romaine	Dandelion
Chicory	Rhubarb	Kale
Cucumber	Sauerkraut	Mustard
Escarole	String beans young	Poke
Eggplant	Summer squash	Spinach
Lettuce	Tomatoes	Turnip greens

B *Vegetables* —Carbohydrate 7 gm protein 2 gm fat negligible per serving

1 exchange = ½ measuring cup = 100 gm

Beets	Peas green	Squash winter
Carrots	Pumpkin	Turnip
Onions	Rutabagas	

List III —Fruits

Fresh, cooked canned or frozen *unsweetened*
Carbohydrate 10 gm per exchange protein and fat negligible

Fruit	*Approximate measure 1 exchange*	*Weight gm*
Apple, 1 small	2 dia	80
Applesauce	½ cup	100
Apricots, fresh	2 medium	100
Apricots dry	4 halves	20
Banana	½ small	50
Berries (blackberries raspberries and strawberries)*	1 cup	150
Blueberries	⅔ cup	100
Cantaloupe*	¼ (6 dia)	200
Cherries	10 large or 15 small	75
Dates	2	15
Figs dried	1 small	15
Figs, fresh	2 large	50
Grapefruit*	½ small	125
Grapefruit juice*	½ cup	100
Grapes	12	75
Grape juice	¼ cup	60
Honeydew melon	⅛ (7" dia)	150
Mango	½ small	70
Nectarines	1 medium	100
Orange*	1 small	100
Orange juice*	½ cup	100
Papaya	⅓ medium	100
Peach	1 medium	100
Pear	1 small	100
Pineapple	½ cup, cubed	80
Pineapple juice	⅓ cup	80
Plums	2 medium	100
Prunes dried	2 medium	25
Raisins	2 tbsp level	15
Rhubarb	(See List II A)	
Tangerine*	1 large	100
Watermelon	1 cup diced 1 slice 3 × 1½	175

*These fruits are rich sources of vitamin C, use at least one serving each day

The Bread Exchanges, List IV, contains bread crackers, cereals, 20 per cent vegetables and 1 cc of cream which is substituted for a bread exchange

List IV —Bread Exchanges

Carbohydrate 15 gm , protein 2 gm fat negligible

Food	*Approximate measure 1 exchange*	*Weight gm*
Bread baker s	1 slice	25
Biscuit roll	2 dia	35
Muffin	2 dia	35
Cornbread	1½ cube	35
Cereals cooked	½ cup cooked	100
Cereals dry (flakes puffed and shredded varieties)	¾ cup scant	20
Rice, macaroni noodles spaghetti	½ cup cooked	100
Crackers		
Graham	2 (2½ × 2½)	20
Oyster	20 (½ cup)	20
Saltines	5 (2 square)	20
Soda	3 (2½ × 2½)	20
Round thin varieties	6–8 (½ dia)	20
Vegetables		
Beans peas dried (cooked) Includes limas navy kidney beans blackeyed cowpeas and split peas etc	½ cant	100
Corn	⅓ cup or ½ ear	80
Parsnips	½ cup	125
Potatoes		
White baked	2 dia	100
White boiled mashed	½ cup	100
Sweet or yam	¼ cup	50
Ice cream vanilla*	⅛ quart	70
Sponge cake no icing	1½ cube	25

* Omit 2 fat exchanges

Meat Exchanges, List V contains meats and meat substitutes, cheese peanut butter and eggs

List V —Meat Exchanges

Carbohydrate negligible protein 7 gm fat 5 gm per serving *Note* All items expressed in cooked weight One or more fat exchanges from the diet may be used to cook or season these foods

Food	*Approximate measure 1 exchange*	*Weight gm*
Meat		
Beef fowl lamb veal (medium fat) liver pork ham (lean)	1 oz	30

Food	Approximate measure 1 exchange	Weight gm
Cold cuts		
Salami, minced ham, bologna, cervelat, liver sausage luncheon loaf	1 slice, 4½" diam × ⅛"	45
Frankfurter (8-9 per lb)	1	50
Fish		
Cod, haddock, halibut, herring etc	1 oz	30
Salmon tuna, crabmeat lobster	¼ cup	30
Shrimp clams, oysters (medium)	5	45
Sardines	3 medium	30
Cheese		
Cheddar type	1 oz	30
Cottage	3 tbsp level	45
Peanut butter*	2 tbsp scant	30
Egg	1	50

* Limit to one serving per day unless adjustment is made to balance carbohydrate content

Fat Exchanges, List VI contains butter, cream, bacon, and substitutes for these

List VI —Fat Exchanges

Carbohydrate and protein negligible, fat 5 gm per serving

Food	Approximate measure 1 exchange	Weight gm
Butter or margarine	1 tsp level	5
Bacon, crisp	1 slice	10
Cream, light sweet or sour—20%	2 tbsp level	30
Cream heavy—40%	1 tbsp level	15
Cream cheese	1 tbsp level	15
French dressing	1 tbsp level	15
Mayonnaise	1 tsp level	5
Oil or cooking fat	1 tsp level	5
Olives	5 small	50

Variety in Diabetic Diets and Food Substitutes —The standard diets prescribed are constructed of a limited number of foods but it is possible by making substitutions to gain a great variety In patients with diabetes of proven mildness, particularly in adults of middle age or older, control of the condition may often be won merely by eliminating sweet foods from the diet, though some restrictions must be made as to such starch-containing foods as bread, rice, and the like If such measures fail to control glycosuria and maintain normal blood sugar level, it is wiser for the patient to use insulin than run the risk of under-nutrition

Weighing foods is desirable for all diabetic patients in the early course of treatment Only by doing so can the diabetic appreciate the significance

of calories in his diet and the possibility of variety in his carbohydrate foods With many mild cases, the experience in weighing food will teach the patient the ability to measure food in household measures or with the eye, which may be sufficient to make good control possible In carrying out dietary instruction, therefore, particularly with a weighed diet, some simple directions are necessary

1 Butter and cream should be weighed for the day before the first meal It then becomes possible to use portions of them in preparing other foods
2 Weighed portions of vegetables and meat should be removed from the family supply and prepared separately
3 Table 86 gives substitutions for vegetables and fruits

Since the introduction of insulin and more generous carbohydrate diets there has been no need for special diabetic foods or special diabetic cooking Saccharin, however, should be mentioned, for it may be used for sweetening beverages or cooked fruits, provided it is added after the cooking has been done If saccharin is cooked, it turns bitter Water-packed fruits are to be used in preference to the ordinary canned products, for widely varying amounts of sugar are added to the latter Though no sugar is added to many of the frozen foods, these naturally contain fairly large amounts of sugar For this reason diabetics should not use frozen fruits without knowing something of the method by which they are prepared

Diabetics may include in their diets peppers, vinegar, spices, extracts of vanilla and lemon, coffee and tea for none of these has significant food value Thin broths may be used between meals or at mealtime, as desired, though they should be avoided in excessive quantity because of their salt and nitrogen content

Recipes —Though at present there is no general teaching of special diabetic recipes in most large hospitals, the two following recipes for diabetics are commonly used in them

Diabetic Mayonnaise

2 egg yolks	1 tablespoon salt
1 quart mineral oil	1 teaspoon paprika
juice of one lemon	1 teaspoon mustard
⅓ cup vinegar	1 saccharine tablet

Beat up egg yolks Add dry ingredients Add small amount of vinegar Mix well and add oil slowly until 1½ cups are added Add rest or oil and vinegar alternately until all is used Lastly add lemon juice and a few drops of tabasco sauce Mix and beat well

Diabetic French Dressing

2 teaspoons mustard	6 cups mineral oil
2 teaspoons salt	3 cups vinegar
1 teaspoon pepper	garlic
3 teaspoons paprika	

Rub bowl well with garlic Mix dry ingredients Beat in mineral oil gradually Add vinegar and beat (Shake well before using)

Bouillon soup may be used without substituting for other foods. Vegetable soups may be made from part of the vegetable allowance and part of the cream and butter allowance.

Minerals.—The importance of certain mineral salts in diabetes has been increasingly recognized. Sodium chloride retention has often explained sudden changes in body weight, loss of sodium chloride during polyuria has sometimes led to such a depletion of body chloride as to bring about anuria. Phosphorus plays an important part in the metabolism of fat and carbohydrate. Salt may be used freely by diabetic patients. If it is withdrawn from the diet, the weight falls and dehydration occurs. When broths are freely given, water is retained in the body. The patient gains not only in weight but in sense of well being. Bacon and ham may add from 5 to 7 gm. to the salt intake. The common excretion of salt in twenty-four hours varies from 10 to 15 gm. per day. Acidosis of long duration reduces the store of alkali, especially in the bones. In diabetic coma the excretion of calcium and magnesium is excessive. Decalcification of bones in diabetic patients is due in part to disuse and in part to acidosis, as well as to diets low in calcium. This is sometimes associated with fractures. Indeed, fractures of the vertebrae or of other bones caused by slight trauma are not infrequent in diabetic patients. Diabetic adults require 0.8 gm. calcium daily and diabetic children 1 gm. A diet that does not include dairy products contains only 0.4 gm. of calcium. But since 90 cc. of milk, 120 cc. of cream, 10 gm. of American cheese, and three eggs contain each 0.1 gm. of calcium, it is easy to bring the dietary calcium up to the required amount. Beet greens, broccoli, cauliflower, chard, dandelion greens, turnip tops are all high in calcium.

The daily iron requirement for diabetics is from 15 to 20 mg. Iron is especially abundant in liver, meat, navy beans, lima beans, eggs, prunes, and whole wheat.

Vitamins.—Table 92 shows the vitamin content of the diet which most moderately active middle aged diabetics are given at the time of their discharge from the hospital, and compares this diet with the daily maintenance requirement of non-diabetic women in regard to vitamins and minerals. Many younger diabetics, needless to say, in full activity receive 2000 to 3000 calories daily with a corresponding increase in vitamin intake.

TABLE 92

	Calcium gm.	*Iron mg.*	*Vitamin A I.U.*	*Vitamin B1 mg.*	*Ascorbic acid mg.*	*Riboflavin mg.*	*Niacin*
Woman (moderately active) daily requirement	0.8	12	5 000	1.0	70	1.4	10
Active diabetic discharge diet (C165 P82 F97)	0.83	16.7	16 000	1.5	256	1.6	15.9

It is estimated that the diabetic diet provides at least 15 mg. of nicotinic acid. The vitamin D requirement of adults has not been estimated either by the National Research Council or by our group. It may be said, however, that the diabetic diet probably supplies the same amount of vitamin D as

the nondiabetic diet, since it contains eggs, butter, and cream The diabetic diet contains, too, the estimated daily normal requirement of both thiamin chloride and riboflavin and 3 times the daily normal requirement of both vitamin A and vitamin C

AVITAMINOSIS IN THE DIABETIC

Unnecessary dietary restrictions in cases of diabetes may lead to avitaminosis if long continued

That a *vitamin B deficiency*, for example might be an etiological factor in the peripheral neuropathy of diabetics was early pointed out by Root[3] and by Wohl in 1926[24]

Subsequently, Fein and his associates[25] found that 'the symmetrical peripheral neuropathy beginning first in and involving primarily, the lower extremities of patients having diabetes mellitus responds to thiamin hydrochloride and in our opinion is due to vitamin B_1 deficiency At the Joslin Clinic, though immediate improvement with thiamin therapy is rarely observed in cases of diabetic neuritis the majority of such cases under such therapy show gradual improvement over a period of several months provided the cases are brought under good diabetic control In these findings, the danger of a diabetic diet restricted with unnecessary severity is implicit At present, uncontrolled diabetes is felt to be the primary cause of diabetic neuropathy

Elderly diabetics especially those in bed with infections, tend to eat sparingly and are liable to subclinical or clinical vitamin deficiencies One must constantly guard against this and supplement their diet with vitamins when necessary

The influence of *thiamin deficiency* upon the blood sugar of human beings has been shown by Williams Mason, Wilder and Smith[26]

In three out of four subjects they studied on a diet low in thiamin for prolonged periods, the blood sugar tolerance curves reached diabetic levels Such changes are temporary however, and do not indicate true diabetes for after thiamin is administered the curves return to normal Although the tolerance for glucose is slightly diminished in avitaminosis B_1, Smith and Mason[7] found no evidence of either exacerbation of the diabetes or increase in insulin requirement in two diabetic patients placed on a thiamin-deficient diet and allowed to develop avitaminosis

Vitamin C is usually found in adequate amounts in the diabetic diet, since fruits are usually prescribed with each meal Sebesta Smith Fernals and Marble[8] studied seventy-seven adult diabetic patients and showed that all uncomplicated cases had normal fasting plasma levels of ascorbic acid Furthermore the patients excreted over 400 mg of ascorbic acid in response to a 1000 mg test given intravenously which evidenced normal storage of vitamin C Diabetics confined to bed with surgical lesions however, tended to show low normal or subnormal values It is possible that, owing to the presence of infection such patients metabolize more vitamin C than is usual Since Lund and Crandon[29] showed that extreme vitamin C deficiency is associated with slowing up or even cessation of wound healing,

it becomes important to see that surgical diabetics *do not* develop even subclinical avitaminosis C

The diabetic diet is generously supplied with leafy green and yellow vegetables as well as with cream, butter, and milk As a result, *avitaminosis A* with night blindness, hyperkeratosis, and xerophthalmia has not been observed among diabetics in the New England Deaconess Hospital

Diabetic children usually receive cod liver oil during the winter months

HYPOGLYCEMIA

The treatment and the prevention of episodes of hypoglycemia due to insulin *constitute a major problem in the management of diabetes* Hypoglycemia, of mild degree may have serious consequences if associated with *other factors affecting* brain metabolism, such as hypoxia, alcohol, or sedatives It is a matter of great concern if an innocent person is imprisoned on the supposition that he or she is intoxicated Nor can the suspicion of epilepsy be dismissed lightly in the case of grave failure of students in a long written or oral examination, or of errors in judgment by directors of a corporation Insulin reactions liable to such misinterpretations are, however, rare in the vast majority of cases insulin hypoglycemia is relieved spontaneously by the normal body mechanisms

Insulin reactions occur with a rapidly falling blood sugar, and are marked by *rather abrupt symptoms of* sweating, nervousness, faintness, hunger, headache, and double vision These easily recognized symptoms occur characteristically with rapid-acting insulin With slow-acting insulins—protamine zinc or NPH or Globin—central nervous symptoms sometimes occur without previous warning and the patient may, therefore, be somnolent irritable, confused, or even unconscious before anyone is aware of the onset of the symptoms

Hypoglycemic reactions due to insulin should not occur among diabetic patients if they are given these careful and repeated instructions

1 Test the urine once or twice daily and reduce the insulin dosage if necessary,
2 Spread meals wisely *so that no long periods without food occur*, eat lunches of from 10 to 15 gm of carbohydrate in the middle of the morning in the middle of the afternoon, and at bedtime,
3 Take extra food if unusual physical exercise has been engaged in

When diabetic treatment is being carried out rapidly, the diet is often necessarily reduced If the carbohydrate intake is reduced below 100 gm per day, smaller doses of insulin must be given at frequent intervals to prevent reactions

Treatment —The first principle in the treatment of hypoglycemia is the urgent necessity of providing immediately a normal carbohydrate supply If carbohydrate is given within a few minutes of the onset of hypoglycemia, then only a small amount such as 10 gm carbohydrate in the form of orange juice candy or bread will suffice If, however, the insulin dose has been excessively large, small amounts of carbohydrate will be entirely insufficient Intravenous injections of 50 per cent glucose solution, are best, especially *if the symptoms—convulsions and unconsciousness*—are severe or

the condition has persisted for more than an hour If the patient is unconscious the intravenous administration of glucose solution should be continued without intermission until the patient either is conscious or shows unmistakable evidences of returning consciousness

If the patient will not swallow glucose can be introduced by intranasal stomach tube, care being taken to avoid introducing material into the lungs Glucose, corn syrup molasses, and honey have all been used Warm liquids are preferable to cold Substitutes such as levulose and cane sugar are not quite as good as glucose

Before the days of insulin, spontaneous hypoglycemia occurred in patients suffering from extreme under- or malnutrition Similar incidents may occur in malnourished patients receiving insulin it is therefore customary to inaugurate treatment with small doses of insulin Hypoglycemia due to functioning adenomata of the islands of Langerhans must be borne in mind In such patients hypoglycemia with overnight fasting and particularly after exercise may induce a variety of psychotic states, as well as the characteristic sweating, nervousness or stupor

Prevention —The prevention of hypoglycemic reactions in a diabetic patient taking insulin depends upon the education of the patient to understand and recognize the characteristic symptoms of hypoglycemia, such as the sudden appearance of weakness sweating hunger nervousness, and trembling a few hours after taking insulin

Reactions occurring early in the morning before breakfast such as are common in cases treated with protamine zinc insulin may be prevented in many instances by adjusting the diet so that food including milk, crackers, or cheese is taken at bedtime This lunch is best planned to contain from 6 to 12 gm of protein The effect of carbohydrate on hypoglycemic reactions is immediate The effect of protein, however since its digestion is slower, is less immediate but the glucose derived from it is therefore available for a longer period of time

Alcohol —At first thought alcohol might seem a good source of calories for the diabetic but though it supplies 7 calories per cc, it contains no carbohydrate protein or fat The use of alcohol is not advisable for diabetics for the following reasons (1) When a diabetic patient is well controlled on a given diet, the introduction of concentrated calories from alcohol results in glycosuria Since alcohol is oxidized by the human body in preference to carbohydrate, protein and fat the caloric requirements are fulfilled before the latter foods are assimilated As a result part of the glucose obtained from them is excreted In this indirect way, alcohol causes glycosuria After a so called appetizer," the patient is more apt to break his diet

DIABETIC COMA

In the development of diabetic acidosis and coma numerous metabolic and nutritional disturbances are involved in various degrees yet all depend upon one central etiologic factor namely, the lack of sufficient insulin

1 Insulin deficiency or ineffectiveness may result from lack of insulin or from conditions which increase insulin resistance, such as acidosis itself Other factors which may contribute to the ineffectiveness of insulin include

it becomes important to see that surgical diabetics do not develop even subclinical avitaminosis C.

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Insulin reactions occur with a rapidly falling blood sugar, and are marked by rather abrupt symptoms of sweating, nervousness, faintness, hunger, headache and double vision. These easily recognized symptoms occur characteristically with rapid-acting insulin. With slow-acting insulins—protamine zinc or NPH or Globin—central nervous symptoms sometimes occur without previous warning and the patient may, therefore, be somnolent, irritable, confused or even unconscious before anyone is aware of the onset of the symptoms.

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1. Test the urine once or twice daily and reduce the insulin dosage if necessary.
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3. Take extra food if unusual physical exercise has been engaged in.

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the condition has persisted for more than an hour If the patient is unconscious, the intravenous administration of glucose solution should be continued without intermission until the patient either is conscious or shows unmistakable evidences of returning consciousness

If the patient will not swallow, glucose can be introduced by intranasal stomach tube care being taken to avoid introducing material into the lungs Glucose, corn syrup, molasses, and honey have all been used Warm liquids are preferable to cold Substitutes such as levulose and cane sugar are not quite as good as glucose

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DIABETIC COMA

In the development of diabetic acidosis and coma, numerous metabolic and nutritional disturbances are involved in various degrees, yet all depend upon one central etiologic factor, namely, the lack of sufficient insulin

1 Insulin deficiency or ineffectiveness may result from lack of insulin or from conditions which increase insulin resistance such as acidosis itself Other factors which may contribute to the ineffectiveness of insulin include

hormonal antagonists, antibodies, toxins, enzymes, or chemical conditions inhibiting enzymatic processes involved in the manufacture of insulin

2 In the presence of ketosis and insulin deficiency, impaired glycogen formation, increasing glycogenolysis, hyperglycemia, glycosuria, and diuresis may be accompanied by loss of electrolytes, with consequent dehydration of both the intracellular and extracellular spaces

3 Increased formation of ketone bodies in the liver, with ketonemia and ketonuria, are the primary and characteristic features of diabetic coma New ideas regarding the formation of ketone bodies from fatty acids, and improved methods for estimation of ketone bodies, both qualitative (measurement in the blood plasma) and quantitative, are giving us a clearer understanding of the mechanisms involved [31-39] The important role of the liver in the production of ketonemia, and lipemia, and the significance of fatty deposits in this organ cannot be exaggerated Failure of the liver is a third factor in diabetic coma—one not yet fully appreciated In the terminal stage of diabetic coma ketone formation may fail and in a case reported by Root[40] and Leech alterations in functional tests of the liver are discussed in this connection

4 Metabolic acidosis, with low bicarbonate and low pH of the blood plasma, results partly from the accumulation of ketones and other acid metabolites in the blood and partly from the loss of mineral cations in the urine

5 Increased tissue catabolism is a feature of considerable current interest It involves the liberation of phosphates and associated cations, especially potassium from the cells into the plasma, and their excretion in urine—unless kidney function is impaired Quantitative data on the nature and amount of metabolic losses of potassium, phosphorus, and nitrogen are being accumulated The total metabolism is greatly increased during insulin deprivation, most markedly so after acidosis becomes severe

6 Dehydration due to the loss of electrolytes is a major problem in treatment It is the loss from the intracellular space which is of chief importance and a special significance is attached to the loss of potassium Its normal concentration in the plasma is from 3 1 to 4 5 mEq /L During diuresis in diabetic coma, potassium is lost in the urine In acidosis a negative nitrogen balance occurs due to the breakdown of protein, and this fact, together with glycogen breakdown accounts for the release of potassium Initially, the blood potassium value may be rather high, but under insulin treatment with the withdrawal of glucose from the blood and the deposition of glycogen—a rather rapid decline of the potassium level may occur Such a deficiency may result in the sudden development of rapid pulse, shallow respiration, the fish mouth expression, electrocardiographic changes, and paralysis of the voluntary muscles

7 Irreversible tissue change is assumed to cause deaths among patients long comatose in spite of treatment or in whom treatment has been long delayed

8 The unconsciousness itself seems to be the result of tissue damage from anoxemia, acidosis, and dehydration, as clearly shown in the studies of Kety[31] and his associates

Since diabetic coma is a condition of acute insulin deficiency, the primary

objective is to ascertain the insulin deposit and give insulin as rapidly as possible to make up the deficiency Insulin brings immediate improvement by

1 The decline in blood sugar level
2 The fall in the level of ketone bodies and the cessation of excessive ketone body formation
3 Decline in protein breakdown as shown by an immediate change in urinary nitrogen excretion
4 Cessation of the excessive potassium loss
5 Retention of water

The excessive molarity of the extracellular fluid during the height of the hyperglycemia of coma is itself a factor in the intracellular dehydration Until sufficient insulin has been given and a decline in the blood sugar level indicates that the insulin resistance has been overcome the administration of extra glucose can do no real good When however the decline in blood sugar levels indicates that insulin action is effective, then the important thing is the administration of food or glucose if mouth feeding is impossible The first objective in washing out the stomach therefore, is to clear the upper alimentary tract and by enema the lower tract, in order that the administration of food—including protein minerals and vitamins as well as glucose—may be begun In a series of 864 cases treated at the Deaconess Hospital mortality rates have steadily declined over the last thirty years as we have steadily increased the rate of insulin administration Whereas formerly as little as 80 units were given during the first three hours of treatment now in the last 153 coma cases 97 received an average of 271 units in the first three hours In Table 93 the methods now used are summarized

TABLE 93 —TREATMENT OF DIABETIC COMA

Joslin Clinic New England Deaconess Hospital

First Hour after Admission

Special nurse preferably experienced in coma treatment for the first few hours

LABORATORY

1 *Urine* —Examine for sugar acetone diacetic acid albumin coma casts and pyuria Catheterize if necessary
2 *Blood* —Test for sugar CO_2 content and non protein nitrogen with emergency report inside the hour White blood count Serum amylase and K

CLINICAL

3 *Search for complications and establish diagnosis*
 A History to explain cause of coma
 B Physical examination noting particularly
 C X ray chest and abdomen when possible
 D ECG (*a*) coronary (*b*) potassium changes
 (*a*) State of consciousness type of respiration pulse rate blood pressure and rectal temperature
 (*b*) Look for soft eyeballs dry tongue dilated stomach cold and mottled skin and impacted rectum
4 *Insulin* —Fifty to 100 units of regular insulin subcutaneously at once for adults In severe cases especially with circulatory collapse give insulin intravenously If blood sugar exceeds 300 mg per 100 cc and if the blood CO content is 9 millimols per liter (20 volumes per cent) or less the dose will need to be re-

livers have become fatty. Glucose feeding is followed by an increase in ketonemia in the same manner as in diabetic coma. A disturbed liver function, so important in diabetic coma, is in itself secondary to and dependent upon insulin deficiency.

Depletion of glycogen stores favors acidosis in the diabetic patient under conditions of fever, infection, or even excessive work and physical exhaustion. With excess work and a rise in the total metabolism, diabetic patients need not only an increase in all the elements of diet in proportion to the increased work, but also an increase in the dose of insulin to make sure that the extra food is normally utilized.

Patients should be taught that *coma occurs because of (1) too much food, (2) too little insulin, (3) an infection.* (1) Too much food may mean deliberate departure from the diet, (2) too little insulin may mean no insulin, its omission, or the discovery of diabetes with onset of coma, which occurs in about 15 per cent of all cases of coma, or (3) the breaking down of body tissue may occur in undiagnosed diabetes, fever, or hyperthyroidism. Irregular adherence to diet exceeds by far any other cause of coma.

Oral Hypoglycemic Agents.—*A planned and constant diet adequate in calories, minerals and vitamins is of basic importance whenever oral hypoglycemic agents are prescribed.* Failure to instruct patients and lack of cooperation on the part of the patients in the matter of diet soon result in the return of glycosuria, blurred vision, pruritus vulvæ and polyuria unless the diabetes is of such extraordinary mildness that in reality no pills were needed. The prescription of such pills in order to avoid the necessity for self-control in order to stay within the prescribed limits for carbohydrate, protein and fat per day is without justification.

Several agents have recently been used to lower the blood glucose level. The arylsulfonylurea compounds include carbutamide (BZ-55), tolbutamide, chlorpropamide and metahexamide. The first and the last of these have been discontinued in this country. Tolbutamide, because of its effectiveness in mild cases, middle-aged or elderly, obese and requiring 20–30 or less units of insulin, is most in use. Toxic symptoms are rare and mild. It is relatively ineffective in severe cases of diabetes in the presence of complications, such as surgery, fever, ketoacidosis and is notably ineffective in juvenile patients unless the patient is in a very early stage or a stage of remission.

The biguanides, including phenethylbiguanide (DBI) and its homologue, have hypoglycemic action. DBI may be used alone in mild early cases or in the elderly and obese patients. It has in a few cases of juvenile diabetes complicated by severe insulin reactions served in conjunction with insulin to stabilize treatment. Thus, some such patients have been able to reduce their insulin dose *materially* while taking DBI. Unfortunately, 25 to 35 per cent of patients do have some side reactions consisting of nausea and vomiting which preclude the use of the drug. In all moderate or severe diabetic patients, the success of DBI and indeed of any oral reagent is likely to be achieved only with good patient cooperation in the carrying out of a proper diet prescription.

Apparently good clinical effects with the use of oral hypoglycemic

agents depend upon the presence of active insulin either endogenous or exogenous The mode of action of these agents is still obscure, although the effect of tolbutamide in stimulating the release of insulin from the pancreas has been accepted as a working hypothesis The well known group of metabolic effects of insulin, including increased glucose uptake and conversion to glycogen adipose tissue and fatty acid synthesis as well as the increased synthesis of protein from amino acid have not been reproduced by any of the oral agents

THE DIABETIC DIET MODIFIED BY DISEASE

The diabetic diet is necessarily subject to various modifications under the influence of numerous diseases to which the diabetic like the nondiabetic, is susceptible Nothing has modified the diabetic diet so much as the discovery of insulin Prior to this discovery the dietary carbohydrate was radically restricted for diabetics and though the fat intake was high during the Naunyn era, the entire diet was restricted during the Allen era It is unfortunate that even today some diabetics who really need insulin are given markedly restricted diets which encourage vitamin deficiencies and generally lower resistance to disease Such diets are often prescribed out of fear of insulin and the hypodermic needle Today insulin allows the diabetic a full normal diet with as much protein and fat and one-half to two-thirds as much carbohydrate as is found in the average nondiabetic diet Once patients are changed to modern methods of treatment with insulin and diet they cannot be persuaded to pursue their former methods again for they realize the great benefits in health and well being to be derived from adequate therapy

Surgery — Although the use of insulin inaugurated modern surgical care of diabetics—first by making possible the prevention or cure of postoperative acidosis and coma and second by prolonging the lives of diabetics to such an extent that a whole generation has entered the period of life in which complications requiring surgery are frequent—the dietary management both before and after operation remains of fundamental importance Actually the preparation for surgery should begin months or years before operation becomes necessary The family doctor or physician should instil in the patient's mind the fact that surgical procedures can be carried out successfully in direct proportion to the cooperation shown by the patient in reporting the lesion early and accepting promptly the surgical advice Furthermore if diabetic treatment has been properly carried out patients will be prepared by adequate nutrition and proper control of the diabetes before operation

Surgical risk is so minimized under modern treatment that selection of patients for operation is now actually made on a basis of the same indications as those for nondiabetic patients no patient need be denied an operation merely because of his diabetes Operative mortality rates for diabetics formerly reached 30 to 40 per cent but recently mortality rates have fallen to levels ranging from 4 5 to 6 1 per cent at the Mayo Clinic (as reported by Wilder) and to a level of only 2 8 per cent for 2762 operations since 1950 at the New England Deaconess Hospital [41, 4]

Preoperative Preparation—When possible, observation for forty eight hours before operation in the hospital with the measured, weighed diet and sufficient insulin to clear the urine of sugar and control acidosis is required Ideally, the patient should go to the operating room with little or no glycosuria, his liver well stocked with glycogen, his blood sugar normal, and his urine free from diacetic acid [43] In the presence of surgical emergency, such criteria cannot be maintained

The following outline recommended for diabetic patients at the Peter Bent Brigham Hospital has proved helpful

1 The diabetes should be well regulated before operation unless the operation is an emergency

2 All operations upon diabetic patients should be performed early in the day, if possible

3 In general, a diabetic patient on the day of operation can safely receive three-fourths of his usual dose of insulin, as outlined below

4 Patients receiving protamine zinc insulin alone may ordinarily receive three fourths of their usual dose before operation This should be followed within two hours by an infusion of 5 per cent dextrose The latter will often be given during operation

5 If NPH insulin is used, three-fourths of the usual dose should be administered in the morning, followed in one hour by a glucose infusion

6 Patients requiring both protamine or NPH and crystalline insulin should be given the full dose of protamine or NPH and one-half the dose of crystalline insulin before operation If the crystalline dose is less than 10 units it may be omitted A glucose infusion should be started within thirty minutes after insulin is administered

7 Patients having operations upon the lower extremities under spinal anesthesia will often be able to retain a liquid or soft diet soon after return from surgery In such cases, insulin is delayed until return from surgery, when three-fourths of the usual dose is given

8 Unless patients are able to retain an equivalent of 100 gm of carbohydrate including the morning intravenous infusion if given, a second infusion of 5 per cent glucose should be administered in the late afternoon

9 It is preferable to give two 1000 cc infusions of 5 per cent glucose rather than a single larger infusion, since the former allows better utilization of the carbohydrate over a wider spread of time

10 Ten per cent glucose infusions are less desirable, since more glucose is lost in the urine

Postoperative Treatment—Upon return from the operating room, the patients who have been under general anesthesia or have undergone abdominal surgery should receive liquid food of the simplest type, such as oatmeal gruel, tea, or ginger ale, or intravenous glucose solution (5 per cent glucose in saline), if mouth feeding is impossible An attempt is made to insure that a patient shall receive from *100* to *120* gm of carbohydrate per day During the next few days, the diet should gradually be increased The feeding schedule should be changed from small feedings every two or three hours to three meals a day, with perhaps a small luncheon of 10 gm of carbohydrate in the form of Uneeda biscuits with broth between Diarrhea is a frequent complication in diabetic patients It is sometimes

caused by a disturbance in the external pancreatic secretion or by irritation of the bowel or by over-coarse foods When the diarrhea occurs in diabetic patients, so much food may be lost that insulin reactions may occur unless the urine is carefully watched and the insulin dose reduced The development of diarrhea in diabetic surgical patients is a warning that special care must be taken in the management of the insulin dose

Allergy —Sensitization to insulin itself such that severe generalized urticarial reactions or even anaphylactic reactions ensue, occurs rarely but may present a serious problem One method for patients with fairly mild diabetes requiring only small doses of insulin is to use a diet which contains so small an amount of carbohydrate that insulin itself is not necessary When, however, the carbohydrate content of the diet is reduced below 50 gm a day nutritional disadvantages outweigh the gain Therefore in general it is better to desensitize the patient by injecting at thirty-minute intervals, doses of insulin, beginning with as little as one ten thousandth of a unit and rapidly increasing the dose The danger of provoking subclinical scurvy with a diet containing very small amounts of carbohydrate is not great unless the diabetes itself is so severely upset that chronic acidosis interferes with nutrition when scorbutic manifestations might be expected

The occurrence of common allergic states including asthma, hay fever, skin eruptions notably urticaria, is certainly no less common in diabetics than in nondiabetics In such cases desensitization with such antigens as eggs milk sea foods, and various inhalants is necessary Diabetic treatment is sometimes complicated by the necessity for using frequent injections of adrenalin or epinephrine

Cardiovascular renal Disease —A new attitude toward the relation between diabetes and premature cardiovascular-renal disease (especially in young patients with diabetes of long duration) is evolving as a result of recent clinical and pathologic studies and with it a new approach to the treatment and prevention of this complication Increasing emphasis is placed upon the changes in the smaller blood vessels, including the venules of the retina the capillaries, and especially the arterioles in the kidneys retina, and pancreas In the series of Bell [44] arteriosclerosis in the renal vessels as elsewhere was four times as frequent and actually this type of lesion was 100 times more frequent in the diabetic than in the nondiabetic group However, follow-up studies of young patients after twenty years of severe diabetes now indicate that the typical sequelæ in the eyes, arteries, and kidneys may be postponed or prevented by early persistent and continuous control of the diabetes The basic requirement is that a diet planned to provide adequate minerals and vitamins as well as a proper combination of carbohydrate, protein, and fat, shall be so well utilized through the early and continued use of insulin that good control of the diabetes, measured in terms of blood and urine sugar excretion, is attained [45–47]

Although early atherosclerotic changes are easily discernible by careful studies in many individuals as early as the second decade it is the unusual frequency of advanced occlusive vascular lesions—chiefly of the coronary vessels and the leg arteries—which provide the main features of diabetic

morbidity and mortality rates However, the most striking demonstration of the influence of diabetes of long duration in the production of vascular disease, particularly in the small vessels, capillaries, venules, and arterioles, is furnished by the records of diabetic patients who survive from childhood for twenty years or more It is in this group that hypertension, chronic vascular nephritis, and severe retinopathy are most frequent Studies of the changes in the smaller blood vessels by Ditzel[48] have indeed indicated alterations in the capillaries of the eyes in patients with very early diabetes, and even in the children of diabetic mothers The capillary changes are widespread, occurring chiefly in the venous portion, and have a common pathology characterized by hyalinization The similarity of staining reactions in the retinal microaneurysms and intercapillary glomerulosclerosis seen in the same individuals was pointed out by Friedenwald[49] The demonstration of mucopolysaccharides by staining and by other means justifies the assumption that these abnormal deposits are in some way related to the restoration of normal metabolism of diabetes These mucopolysaccharides are found as constituents of the ground substance, the basement membrane of capillaries, and the like They are found in other conditions besides diabetes, but at present it is possible to conceive that most of the pathologic alterations of diabetes represent disorders in the metabolism of the simple polysaccharides such as glycogen, or the complex ones such as the mucopolysaccharides Also, the study of the serum lipoproteins in diabetic patients of long duration indicates that the disturbance also involves those aggregations of protein and lipoid substances so carefully studied by Gofman

The prevention of premature vascular disease is based upon (1) the control of body weight within normal limits and reduction of the obese, (2) a diet carefully planned to provide adequate mineral, vitamin, and caloric content, (3) the attempt to control diabetes each and every day by daily tests of the urine and frequent tests of the blood, in order that one may be assured that the daily balance between the insulin supplied by the patient s own pancreas and insulin taken by needle shall be sufficient to provide for utilization of the food taken

The important components of the diet favoring the development of atherosclerosis are thought at present to be the lipids with emphasis upon the fatty acids derived from animal fat in contrast to vegetable fat It is seldom necessary to reduce the fat far below normal levels, in most diabetics, the mount of fat fed will vary from 75 to 100 gm per day The part played by meat in producing arteriosclerosis is entirely speculative Stefanson lived for months on a pure meat diet without ill effects upon blood pressure or kidney function A diabetic patient who takes 1 gm of protein per day per kilogram and avoids obesity will hardly be in error

In a series of some 400 diabetic patients whose diabetes began in childhood or before the twenty-fifth year, studies of the relation of lipoprotein and cholesterol levels to vascular changes showed clearly that those patients under the poorest dietetic control had the greatest incidence of cardiovascular-renal changes and the most abnormal lipoprotein and cholesterol levels In a special group of 188 patients whose diabetes had lasted from a minimum of twenty years to a maximum of twenty-nine years, over

40 of the patients had absolutely no retinal lesions at the end of twenty to twenty-five years Those patients under good control showed no severe retinal lesions, and in no case was the typical Kimmelstiel-Wilson or diabetic nephropathy present On the other hand those patients whose control had been carried out without daily testing of urine without blood tests, and who had had either some acidosis or coma, showed the beginning of Kimmelstiel-Wilson lesions in 25 per cent of the cases Retinal lesions were more frequent This group of patients showed clearly that it is possible to postpone or prevent the malignant retinal and kidney lesions by adequate control of the diabetes

Complications of Pregnancy — The occurrence of pregnancy in a diabetic woman raises several questions of vital importance in her treatment Acidosis was the complication most to be feared in the days before the discovery of insulin At present, no diabetic mother should die of acidosis since insulin should be used for all pregnant diabetic women except the mildest cases control of acidosis by this means is certain The total metabolism is elevated by the growth of the fetus Glycogen stores in the mother are likely to be depleted by vomiting Actually, the carbon dioxide combining power of the plasma is frequently low in the pregnant woman, so that acidosis does develop easily Toxemia and eclampsia both of which cause fetal death are the main complications in diabetic pregnancies

Studies at the Joslin Clinic between January 1 1936 and 1939, by Priscilla White[50] and her associates emphasize the importance of hormonal dietary and insulin treatment in the control and prevention of toxemia during pregnancy A liberal carbohydrate allowance of from 150 to 250 gm per day, protein 2 gm per kg, and fat to complete the caloric prescription of 30 calories per kilogram of body weight are recommended Careful control of increases in body weight are emphasized Six rules for management of the pregnant diabetic woman have been developed as follows

(1) Classify the patient for fetal and maternal hazard
(2) Treat the diabetes to achieve the best possible chemical control
(3) Install measures to prevent or correct edema and hydramnios
(4) Give sex hormone therapy except in borderline diabetes requiring no insulin
(5) Time the delivery early
(6) Provide special care for the infant in the immediate postnatal period

Late in the course of pregnancy the diets in White's cases were supplemented with vitamins including vitamin E and vitamin K The sodium chloride intake was reduced The use of both protamine zinc and crystalline insulin was routine

Wilder[51] stresses nutritional deficiency as an important factor in producing a condition simulating toxemia in pregnancy He cites an extraordinary case with glycosuria, albuminuria hemorrhagic retinitis, and edema of the optic discs relieved by the administration of large quantities of thiamin chloride

Hyperthyroidism — The development of hyperthyroidism may have the most serious consequences upon diabetics The effects of hyperthyroidism on carbohydrate metabolism seem to be at least two first, both the

storage of glycogen in the liver and its release are interfered with, second, an antagonism develops between the thyroid secretion and insulin At any rate, during hyperthyroidism in a diabetic of moderate degree, the amount of insulin required may be very greatly increased Indeed, diabetic acidosis and profound coma may develop with extraordinary rapidity

Treatment —The effects upon the diabetes as well as upon the hyperthyroidism following the administration of iodine solution in the form of Lugol's Solution or the use of radio-active iodine are often dramatic The basal metabolism rate is lowered and at the same time tolerance for carbohydrate improves In general, in cases of hyperthyroidism, particularly during the period of preparation for the operation which is always recommended, the dietary carbohydrate is somewhat increased Usually our patients have received from 170 to 200 gm a day but not more Glucose solution is given both before and after operation in the toxic cases

Gastro-intestinal Conditions with Diabetes —When diabetes is complicated by the appearance of gastro-intestinal disease one of the first considerations is how one can prescribe the diet indicated for the gastro-intestinal disorder and at the same time satisfy the diabetic diet requirements [6]

Peptic Ulcer —A dietary regimen based upon the Sippy diet provides 1 ounce each of milk and 20 per cent cream every hour If this 2-ounce mixture is given from 7 00 A M to 9 00 P M, a total of 40 gm of carbohydrate, 30 gm of protein, and 110 gm of fat, totaling 1,270 calories, is furnished Such a low-carbohydrate, high fat diet can be prescribed safely for a short time, especially since cereals, toast, and dilute orange juice may soon be added to raise the carbohydrate to 100 to 120 gm During the first few days, the insulin dose may have to be decreased, owing to the small carbohydrate intake, but this is partly offset by the rest in bed which is ordinarily advised

A typical convalescent Sippy diet might contain

Breakfast	*gm*	*Dinner*	*gm*	*Supper*	*gm*
Toast	30	Bread	30	Bread	30
Butter	10	Butter	15	Butter	15
1 soft boiled egg		Chicken	75	Lamb	75
Oatmeal	15	Baked potato	60	Rice	60
Milk	120	Puréed peas	150	Beets	150
		Baked custard	120	Baked apple	105
		Milk	120	Milk	105

This diet is usually supplemented with a three-ounce mixture containing milk and cream, 1½ ounces each, at 10 00 A M, 3 00 P M, and 10 00 P M In this way, the patient receives 162 gm carbohydrates, 96 gm proteins, 119 gm fats, 2,103 calories and satisfies his caloric needs Naturally, very sweet desserts allowed in the usual peptic ulcer diet, such as sponge cake and angel cake, must not be included As described earlier, substitutions may be made freely in so far as permissible from both an ulcer and diabetic standpoint

When increasing the convalescent Sippy diet by the addition of eggs, cereal, and toast during the first two weeks of treatment, the insulin dosage

may also need augmenting In general, the carbohydrate content should not exceed 200 to 250 gm daily, and, in severe diabetes, had best not exceed 200 gm The age, weight, and stature of the patient must be given consideration

Vomiting —As with nondiabetics, the etiology of the vomiting should be determined when possible If diabetic acidosis is the cause, the established methods of treatment including large doses of insulin, should be pursued If, however, the diabetic repeatedly vomits from any other cause than acidosis, it is imperative (1) to supply nourishment and (2) to prevent acidosis from excessive use of stored fat[5] This can be done by means of intravenous dextrose 5 per cent in saline or water, although in some cases subcutaneous injection may be preferable The morning dose of insulin must be given with supplementary doses of crystalline insulin as necessary

Once some foods can be retained, a simple bland diet in small amounts can be prescribed Cereal gruel toast crackers milk, and ginger ale usually head the list for this kind of diet Orange juice should be avoided, since it increases peristalsis The food is thereafter gradually increased until the whole regular diabetic diet is resumed

A diabetic must never omit insulin because he is prone to vomit If his urine is sugar-free, the dosage may need to be reduced, but since most frequently the disorder that causes the vomiting also *accentuates the diabetes*, even larger doses of insulin are often imperative to prevent acidosis

Diarrhea —Diarrhea must always be considered seriously in a diabetic, for with it there is a loss of fluids and electrolytes starvation or semistarvation and a tendency to acidosis

As in nondiabetics, ulcerative or mucous colitis typhoid amebic or bacillary dysentery, malignancy of the colon, and other serious disease must be considered

Peculiar to diabetes, however, is a specific type of diarrhea, labeled diabetic diarrhea, which occurs during the night but not usually during the day This type is often dramatically relieved by the parenteral injection of crude liver extract

Absence of free hydrochloric acid is common in diabetes of long duration In a small number of cases, diarrhea or a tendency to diarrhea may develop but relief may be obtained occasionally by administering dilute hydrochloric acid with meals

As with vomiting if diarrhea greatly interferes with the absorption of nourishment, glucose parenterally is indicated Should this method of feeding be employed over a period of time, the administration of vitamins must be included

Diarrhea, though it may favor the development of acidosis especially if accompanied by fever, may on the other hand also cause an insulin reaction when there is failure to absorb food from the intestines Consequently during diarrhea frequent urine and blood sugar determinations are necessary to adjust the insulin dosage Any diabetic with moderate or severe diarrhea should be hospitalized

Constipation —Constipation is a frequent complaint among diabetics especially older ones One must be sure that a carcinoma of the colon or rectum does not underlie this symptom

The diabetic diet tends to prevent constipation by including a large number of 3 and 6 per cent vegetables high in roughage and a liberal amount of fruit, especially oranges, which tend to stimulate peristalsis

Simple methods should first be tried to correct constipation and the laxative habit avoided Regularity in going to the toilet at the same time each day is helpful Regular exercise and the consumption of a large quantity of liquids are simple time-proved remedies Drinking two glasses of water half an hour before breakfast is beneficial In the older patients who are unable to take much exercise, abdominal kneading, leg rolling, abdominal compression, and trunk rolling may prove satisfactory

If laxatives are necessary, the milder ones, such as mineral oil, agar agar, and compound rhubarb pills should be used first If patients are made to realize that, for some individuals, one bowel movement every two days is adequate much ease of mind for the patient will result Some insist that without laxatives they do not have results, and hence take drugs every night In such cases, the colon eventually becomes atonic, and, if long continued, irreversible loss of tonicity supervenes

Diabetic Retinitis —Some of the ocular symptoms observed in diabetic patients, notably the temporary blurring of vision or lipemia retinalis are readily amenable to treatment and control of the diabetes It is the increasing frequency of serious and permanent visual deterioration due to diabetic retinitis and especially to the increasing frequency of retinitis proliferans which is changing objectives in treatment today The simple retinitis, consisting of hemorrhages exudates and the microaneurysms of diabetes is frequently followed particularly in the severe diabetes which has its onset early in life by the proliferative phase The course, once proliferative retinopathy has developed, is unfortunately rapid and sooner or later associated with the typical diabetic nephropathy In a recent analysis[54] of 847 cases of proliferative retinopathy, it appeared that this ocular lesion has become almost pathognomonic of severe diabetes in the adult In the series reported, rarely did the lesion begin until diabetes had been present 8 years or more and the average was nearly 17 years *In no case* did retinitis proliferans develop in a patient whose diabetes had been adequately treated with insulin since the onset of diabetes and with a carefully planned diet, with the patient's cooperation so that the urine was tested daily in the attempt to become sugar free and regular supervision by a competent physician carried out It seems clear that the retinal and renal lesions of severe diabetes sooner or later go hand-in hand and that somewhere in the relationship between insulin other hormones, vitamins and enzymes in the metabolism of food will be found the explanation for this malignant disorder thanks to the intensive investigation now going on in many laboratories At present the prevention of retinitis and the proliferative retinopathy is clearly possible if the control of diabetes from the onset of the disease is meticulously maintained under adequate medical supervision

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Chapter 24

Nutrition in Renal Disease

By Howard M. Odel

"Dietetic practice in the management of glomerular nephritis today is in a state of chaos. As an example, the different proposals for the management of the initial stage of the disease may be cited. There is one justly famed authority who gives his patients no water as well as no food. Yet there are other reasonable people who believe that a great quantity of water, much more than the patient wants, is beneficial. Some think it important to see that a more than adequate quantity of protein is consumed, while others, apparently just as sane, advocate as far as possible a protein free diet. The result, of course, is that many sensible people who have no basis for an opinion of their own adopt a nihilistic position and let their patients have anything they fancy. It is important to recognize that this extraordinary state of disorganization is not due to a lack of knowledge of the disease itself, for there is a widely extending consensus as to its nature and course. Nor is it due to any misunderstanding of the principles of nutrition which today are more firmly based on practice than ever before. It is quite clearly a dietetic disorientation due to lack of theory." To a large degree, the above statements are as apropos today as they were twenty years ago, when they were made by Addis.[1]

The all-important place of proper dietetic practice in the management of renal disease is more evident at present than it ever has been. Basic concepts in the realm of renal physiology have been emphasized, revised or expanded in the past few years and from this increasing knowledge new dietary principles have been developed that form an important adjunct to the treatment of patients suffering from one of the diseases related to the kidneys.

RENAL FUNCTION

In simple terms, the function of the kidney is the secretion and excretion of urine. It is the avenue of elimination for 40 to 60 per cent of all water liberated from the body. It excretes the waste products of the breakdown of protein—urea, uric acid, creatinine and sulfate—the retention of excess amounts of which is found in the uremic state. It is an important factor in the preservation of the normal acid base balance of the organism by the excretion of excessive amounts of acid. It helps to maintain that normal physiochemical state of body fluids responsible for osmotic pressure. When this balance is disturbed, one of two phenomena results, namely, edema or dehydration.

None of the many classifications of renal disease is entirely inclusive or satisfactory. For this reason, in the following discussion the term "neph-

ritis" is used in its broadest sense, no attempt will be made to specify the different types of vascular, inflammatory or degenerative diseases of the kidney. Lueth[4] has stated that since no specific therapeutic agent is available, treatment of nephritis is confined chiefly to regulation of water balance, adjustment of body electrolytes, especially sodium, chloride and potassium, and close supervision of the diet in an effort to maintain optimal nutrition. Proper dietary guidance plays a role of paramount importance in the management of this group of diseases. From the patient's standpoint it is necessary only to regard nephritis as a condition in which one or more of the functions of the kidney are impaired. The diet is planned, in so far as possible, to spare the damaged kidney and to avoid undue strain on its excretory function.

PROTEIN-RESTRICTED DIETS

Just as the function of the heart is to move blood the kidney must work to move water. Work is required by the heart in performing its major function because blood must be moved against the resistance of a filled vascular tree. The kidney, however, moves water from the glomerular filtrate within the tubular system across the filtering surface of the tubular epithelial cells and into the peritubular capillaries. Work is required in this process because this movement must be made against the resistance of osmotic pressure exerted by the constituents of the filtrate itself, which pressure is ordinarily greater than that of the blood in the extratubular capillaries. Unless work is done the movement of water will be in the opposite direction.

TABLE 94.—APPROXIMATE COMPOSITION OF DIETS RESTRICTED IN SODIUM

		Content of Protein in Diet, gm			
Constituent	*Unit*	*40**	*70*	*100*	*130*
Protein	gm	40	70	100	130
Fat	gm	110	125	130	140
Carbohydrate	gm	270	210	200	210
Calories		2 210	2 240	2 330	2 660
Calcium	mg	930	990	1 250	1,650
Iron	mg	11	13	16	18
Sodium†[4]	gm	0 4	0 5	0 7	0 8
Potassium[4]	mg	3 180	3 470	4 020	4 680
Vitamin A	I U	9 900	9 600	10 000	10 000
Thiamine	mg	1 1	1 1	1 3	1 4
Riboflavin	mg	1 5	1 8	2 4	3 1
Niacin	mg	8	13	16	19
Ascorbic acid	mg	210	185	185	190
Water‡	cc	1 470	1 420	1 700	1 730

* The diet containing 40 gm of protein includes less than the recommended dietary allowances of the National Research Council for niacin, riboflavin, calcium and iron. Supplemental calcium and iron and a half vitamin supplement should be ordered by the physician to compensate for these discrepancies.

† Each of the above diets will contain approximately 1 5 gm more sodium if the foods are cooked with the sodium chloride necessary for seasoning.

‡ The water listed is exclusive of that in tea and coffee.

TABLE 95 —FOODS INCLUDED AND EXCLUDED IN RESTRICTED SODIUM (0 4 TO 0 8 GM) DIETS IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Type of food	*Included*	*Excluded*
Beverage	Carbonated beverages not more than ½ pint daily, cereal beverage, coffee, tea, milk 1 pint daily, including that used in cooking	Soft water cultured buttermilk
Bread	Bread made without baking powder baking soda or salt	Bread and crackers made with baking powder baking soda or salt pancakes, waffles
Cereal	Cooked cereals prepared without salt Puffed Rice, Puffed Wheat Shredded Wheat	Dry prepared cereals except those included
Dessert	Custard or ice cream made from milk and egg allowance, gelatin desserts made with plain gelatin and foods allowed, unsalted fruit pie, puddings made from foods allowed, desserts made without salt baking powder, baking soda or egg white	Desserts prepared with salt baking powder baking soda or egg white, commercial gelatin desserts commercial ice cream rennet desserts
Fat	Unsalted butter, cream ¼ cup daily salad oil, unsalted salad dressing vegetable fat, unsalted shortening	Salted butter, bacon fat salted salad dressing salted margarine
Fruit	Any juice, canned cooked or raw fruit	Dried fruit containing sodium benzoate
Meat, egg or cheese	Meat or fowl in allowed amounts prepared without salt, fish except those excluded, oysters except frozen heart, liver, eggs in allowed amounts	Salted or smoked meats fish or fowl, salted canned meats fish or fowl, frozen fillets of fish, except whitefish pike and lake trout, shellfish except oysters, glandular meat except liver and heart, all cheeses
Potato or substitute	Potato macaroni noodles rice spaghetti	Fried potato potato chips hominy
Soup	Unsalted broth or cream soup made from milk allowance	Any other
Sweets	Pure sugar candy jam jelly or marmalade made without sodium benzoate sugar, syrup, honey, molasses	Jam or jelly containing sodium benzoate, candy except that included
Vegetable	Any canned cooked or raw vegetable or juice prepared without salt except those excluded beets beet greens celery chard dandelion greens kale and spinach no more than one serving daily	Vegetables prepared with salt, frozen corn lima beans or peas and mixtures of frozen vegetables containing corn lima beans or peas
Miscellaneous	Chocolate cocoa unsalted white sauce herbs spices and vinegar in moderation unsalted nuts unsalted peanut butter unsalted popcorn	Catsup chili sauce gravy horse radish mustard, olives salted peanut butter salted pickles salted popcorn relishes salt salted nuts chemically softened water

Under ordinary circumstances, as much as 90 per cent of the dissolved constituents in the urine may be accounted for by urea and sodium chloride. It has been shown that work done by the kidney varies as the rate of excretion and it would appear, therefore, that a reduction in the rate of excretion of salt and urea would be of prime importance in reducing the work of the kidney. Actually it has been demonstrated that work required for the excretion of sodium chloride is small in amount, whereas it has been calculated that approximately 76 per cent of the kidney's work ordinarily is devoted to the excretion of urea.[3]

TABLE 96.—FOODS INCLUDED AND EXCLUDED IN THE 2.0-GM. SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Type of food	*Included*	*Excluded*
Beverage	Carbonated beverage, cereal beverage, coffee, milk, milk drinks, tea	None
Bread	Any, with emphasis on whole-grain or enriched bread, except those excluded	Salted crackers, soda crackers
Cereal	Any, with emphasis on whole-grain or enriched cereal	None
Dessert	Cakes, cookies, custards, gelatin desserts, ice cream, rennet desserts, puddings, sherbets	Rich pastries
Fat	Butter and substitutes, cream, salad dressing, salad oil, shortening, fortified margarine	Bacon fat
Fruit	Any fruit or juice, including one citrus fruit or other food high in vitamin C daily	None
Meat, egg or cheese	Any meat, fish or fowl except those excluded, eggs, cottage cheese, cream cheese	Salted or smoked meats, fish or fowl, bacon, cheeses other than those included
Potato or substitute	Potato, hominy, macaroni, noodles, rice, spaghetti	Fried potato, potato chips
Soup	Cream soup	Bouillon, broth, soups made with broth
Sweets	Candy, honey, jam, jelly, sugar, syrup, molasses	None
Vegetable	Any except those excluded	Salted pickles, sauerkraut
Miscellaneous	Chocolate, cocoa, white sauce, unsalted nuts, spices and vinegar in moderation, herbs, peanut butter, unsalted popcorn	Gravy, salted nuts, olives, salted pickles, salted popcorn, relishes, salt, except small amount in cooking

Since urea is one of the major end products of the breakdown of protein, since increased ingestion of protein results in increased formation and excretion of urea, since the major avenue for excretion of urea is through the kidneys, since it has been shown that the bulk of the kidney's work is involved in excreting urea, and since average or additional work inflicted on a diseased organ may result in additional damage or injury to that organ, therefore, if the work of the kidney is to be reduced to a minimum, the content of protein in the diet must be carefully considered. On these

Earlier teachings stated that the minimal amount of protein that would keep a patient in positive nitrogen balance was approximately 1 gm per kilogram of body weight Kempner,[5, 6] however, has shown that many patients maintained on a diet of rice and fruit for a prolonged period remain in positive nitrogen balance even though the diet contains but 20 gm of vegetable protein daily He has shown further that the concentration of urea nitrogen in the twenty-four-hour volume of urine excreted by patients receiving a rice diet is about 20 per cent less than the concentration noted in patients receiving a semistarvation diet, from this observation, he considered that the diet greatly reduces the work of the kidney Tables 98 and 99 illustrate the effect of restriction of protein in the diet on the level of urea in the blood In Table 98 a patient suffering from severe essential hypertension had a value for urea of 104 mg per 100 cc of blood on admission The next day he began eating a diet of rice and fruit, eighteen days later, the urea had decreased to 66 mg Table 99 shows the course over a period of twenty months of a patient suffering from severe diffuse arteriolar disease with hypertension group 4 (malignant hypertension) and renal insufficiency Although the rice-fruit and weighed low-sodium diets had no effect on the blood pressure in this patient, the influence of diets greatly restricted in proteins is striking It is of interest to note also that in these 2 patients, great restriction of salt and protein in the diet resulted in neither hypochloremia nor hypoproteinemia

Borst,[7] in 1948 devised a diet essentially devoid of protein, potassium and phosphorus, and consisting of a pudding composed of water, custard powder (cornstarch), sugar and butter (Table 100) The diet admittedly is

TABLE 100 —HIGH CARBOHYDRATE HIGH FAT PROTEIN FREE DIET (BORST[7])

	Amount	*CHO, gm*	*Protein gm*	*Fat gm*	*Sodium, gm*	*Calories*
Sugar	150 gm	150 0				600
Butter*	100 gm			81 0	0 980	729
Cornstarch	150 gm	130 5	0 75	0 3	0 006	525
Water	Q s to 1,500 cc					
Total	1 500 cc	280 5	0 75	81 3	0 986	1 854

* Unsalted butter containing 0 005 gm of sodium per 100 mg (analysis by Mead Johnson & Company Research Laboratories 1947)

monotonous and unattractive Borst predicated the beneficial results of this diet on the complete restriction of protein with sufficient carbohydrate and fat to prevent breakdown of endogenous, or body, protein Figures 59 and 60 illustrate the use of the Borst diet in a patient suffering from oliguria and acute renal failure

The patient was admitted to the ... al in an emergency status, having
experienced a... pression of ... days previously On admission,
the blood ... d 158 ... and the value for creatinine was
12 mg ... e patie ... ed obesity and generally poor
condition, ... excretion, such as extra
corporeal ... unwise, even though

Borst diet

20 gm protein daily

40 gm protein daily

Creatinine in blood

Urea excreted in urine

Blood urea

Oral fluid intake

Parenteral fluid intake

Urine excretion

Creatinine in blood mg per 100 cc

Blood urea mg per 100 cc

Urea in urine mg per 100 cc

Days in hospital

Fig 59 —Effect of Borst diet on urea and creatinine in patient who had oliguria and acute renal failure See text for details

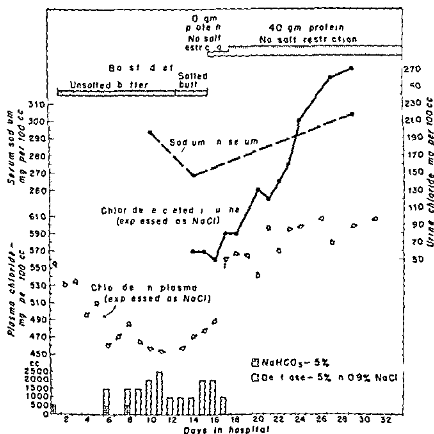


Fig 60 —Effect of Borst diet on sodium and chloride in plasma and urine in same patient whose findings are depicted in Figure 59 See text for details

the renal lesion was considered to be reversible Accordingly, a Borst diet was given during the next sixteen days At the end of this period, the values for urea and creatinine were decreasing and the patient was excreting daily volumes of urine in excess of 1,500 cc He then began to receive a diet containing 20 gm of protein daily, which was later increased to 40 gm daily At the time of dismissal, on the thirty third hospital day, he was instructed concerning a diet containing 70 gm of protein daily (Tables 96, 97 and 101) with no restriction of salt Figure 60 indicates the restriction of salt imposed during his illness, as well as the values for chloride in plasma and urine

TABLE 101 —APPROXIMATE COMPOSITION OF 2 0 GM SODIUM DIET

	Amount
Protein	70 gm
Fat	125 gm
Carbohydrate	200 gm
Calories	2,190
Calcium	1 020 gm
Iron	13 mg
Sodium*	2 0 gm
Potassium*	3 420 gm
Vitamin A	9,400 I U
Thiamine	1 1 mg
Riboflavin	1 9 mg
Niacin	13 mg
Ascorbic acid	130 mg
Water*	1 340 cc

* Exclusive of that in tea and coffee

Bull and associates,[8] in 1949, modified the Borst program, substituting peanut oil for butter Their modification (Table 102) has the advantage of being liquid rather than semisolid in consistency, which makes possible its administration either orally or by continuous drip through a nasal tube into the duodenum The principles involved and the indications for

TABLE 102 —HIGH CARBOHYDRATE HIGH FAT, PROTEIN FREE DIET (BULL[8])

	Amount	CHO gm	Protein gm	Fat gm	Calories
Dextrose	400 gm	400			1 600
Peanut oil	100 gm			100	900
Acacia	Q s to emulsify				
Water	Q s to 1 000 cc				
Total	1 000 cc	400		100	2 500

use of the Bull formula are the same as for the Borst diet In numerous cases of acute urinary suppression, the program has been found to be helpful in sparing damaged kidneys during the phase of renal insufficiency and retarding or preventing the onset of the uremic state At present two products are being marketed commercially (Tables 103 and 104), each of which has been prepared with some modifications according to the Bull

formula Clinical experience has afforded repeated examples of how the progress of renal insufficiency and retention of nitrogen with associated symptoms of uremia may be retarded by giving such a patient a diet low in protein but high in carbohydrate and fat The value of such programs, however, appears to be in the treatment of patients in whom such drastic measures may be necessary for limited periods only For patients suffering from chronic renal insufficiency, it is doubtful that protein in the diet ever should be restricted to less than 40 gm daily

TABLE 103 —HIGH CARBOHYDRATE HIGH FAT PROTEIN FREE FORMULA (LIPOMUL*)

	Amount	*CHO gm*	*Protein gm*	*Fat gm*	*Calories*
Peanut oil	189 2 gm			189 2	1,702 8
Dextrose	47 3 gm	47 3			189 2
Emulsifier and water	Q s to 473 cc				
Total	473 cc	47 3		189 2	1 892 0

* The Upjohn Company Kalamazoo Michigan

TABLE 104 —HIGH CARBOHYDRATE HIGH FAT PROTEIN FREE FORMULA (EDIOL*)

	Amount	*CHO gm*	*Protein gm*	*Fat, gm*	*Calories*
Coconut oil	250 gm			250	2 250
Sucrose	62 5 gm	62 5			250
Emulsifiers preservatives and water†	Q s to 500 cc				
Total	500 cc	62 5		250	2,500

* Schenley Laboratories Inc Lawrenceburg, Indiana

† Glycerol monostearate 1 5% polyoxyethylene sorbitan monostearate 2 0% sodium benzoate 0 1% butylated hydroxyanisol 0 01%, and sodium ethylene diamine tetra acetic acid 0 05%

HIGH-PROTEIN DIETS

In chronic nephritis with nephrotic features, or chronic nephrosis, the kidneys usually are able to function adequately in the excretion of urea and other metabolic waste products but there is a serious depletion of protein in the plasma (hypoproteinemia) This is due in part to loss of protein in the urine but also is due undoubtedly to faulty absorption or utilization or both of ingested protein The principal clinical manifestation of this disease is varying degrees of edema of the viscera and peripheral tissues, many of the associated symptoms being caused by interference in function due to increased edema in tissue spaces The mechanism of formation of edema in this condition appears to depend on a pronounced decrease in the colloidal osmotic pressure of the blood which tends to hold fluid in the

blood stream Under normal circumstances, this osmotic pressure is exerted primarily by the total protein in the plasma, the albumin fraction exerting a greater osmotic effect than the globulin fraction When the nephrotic state exists, the concentration of protein in the plasma is greatly reduced, the most striking decrease being in the concentration of albumin A large part of the loss of protein may be explained by the amount of albumin excreted in the urine in such patients, but in many instances, levels of plasma proteins encountered appeared to be lower than those explicable solely by the amount of protein lost in the urine With the decrease in colloidal osmotic pressure in the blood, the opposing hydrostatic pressure of the blood tends to drive fluid from the blood stream into the tissues

The proper amount of protein to be administered in the diet of such patients has been a subject of concern for some time In the nephrotic state, the prevailing opinion at present is that, if the kidneys are capable of excreting nitrogen in a normal manner, the patient should be given a diet high in protein (100 to 130 gm daily) in an attempt to replace depleted plasma proteins, thereby increasing the colloidal osmotic pressure of the blood However, high-protein diets do not appear to exert any immediately evident effect on the level of plasma proteins, and usually it is necessary to resort to intravenous administration of one of the expanders of plasma volume, such as acacia, gelatin or dextran, to produce temporary increase of the plasma colloidal osmotic pressure to levels that are effective for diuresis Tables 105, 106 and 107 show the approximate composition, types of food included and excluded, dietary pattern and sample menus for diets containing 100 and 130 gm of protein daily Although these diets are described as being poor in sodium, the sodium content of the diet containing 100 gm of protein cannot be restricted to less than 0 7 gm (1 8 gm of salt) daily because of the sodium in the milk, meat and eggs included in such a diet If it is desired to increase the protein content of the diet to 130 gm daily, the minimal sodium content of the diet necessarily increases to 0 8 gm (2 0 gm of salt)

It may be that large amounts of protein ingested by nephrotic patients pass through the gastrointestinal tract, with a large proportion excreted in the feces because of inadequate intestinal absorption On the other hand, it may be that proteins are broken down and absorbed across the intestinal wall in a normal manner but are inadequately utilized by the liver and thus not rendered suitable for replacement of plasma proteins For these reasons, plus the fact that a high-protein diet imposes an additional load on damaged kidneys, Addis[9] was of the opinion that the patient suffering from nephrotic edema with low levels of plasma proteins should be given approximately 1 gm of protein per kilogram of body weight daily, to which is added a quantity equivalent in amount to that lost in the urine in twenty-four hours

On rare occasions, the clinician may encounter a nephrotic patient in whom, in addition to massive peripheral edema and accumulation of free fluid in the serous cavities of the body, extensive edema of the walls of the gastrointestinal tract occurs to such a degree that it interferes seriously with normal gastrointestinal function Such a patient finds it extremely difficult to eat solid foods, especially meat, and to take large quantities of

TABLE 103.—DIETARY PATTERN AND SAMPLE MENU FOR RESTRICTED SODIUM DIETS IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Dietary pattern	*Sample menu*	*Diets Using* Sodium 0.7 gm, Protein 100 gm: *Weight* gm	*Approximate measure*	*Diets Using* Sodium 0.8 gm, Protein 130 gm: *Weight* gm	*Approximate measure*
	BREAKFAST				
Fruit*	Grapefruit	100	½ medium	100	½ medium
Cereal, unsalted*	Unsalted cereal	15 (dry)	½ cup (cooked)	15 (dry)	½ cup (cooked)
Egg	Soft-cooked egg	100	2	100	2
Bread unsalted*	Unsalted toast	25	1 slice	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square	7	1 square
Beverage*	Coffee		1 cup		1 cup
Cream	Cream 20%	75	⅓ cup	75	⅓ cup
Sugar	Sugar	15	1 tablespoon	15	1 tablespoon
	DINNER				
Meat unsalted*	Unsalted roast beef	120	4 ounces	120	4 ounces
Potato, unsalted*	Unsalted buttered potato	100	½ cup	100	½ cup
Vegetable unsalted*	Unsalted buttered new cabbage	75	½ cup	75	½ cup
Salad*	Sliced tomato	75	½ medium	75	½ medium
Fruit*	Sliced orange	100	1 medium	100	1 medium
Beverage*	Milk	240	½ pint	240	½ pint
Bread unsalted*	Unsalted bread	25	1 slice	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square	7	1 square
	SUPPER				
Meat unsalted*	Unsalted lean cold beef	C0	2 ounces	120	4 ounces
Potato or substitute unsalted*	Baked potato with unsalted butter	100	1 medium	100	1 medium
Vegetable unsalted*	Unsalted buttered green beans	75	½ cup	75	½ cup
Salad*	Celery and carrot sticks	60	3 to 4 of each	60	3 to 4 of each
Fruit*	Sliced banana	100	1 medium	100	1 medium
Beverage*	Milk	240	½ pint	240	½ pint
Bread, unsalted*	Unsalted bread	25	1 slice	25	1 slice
Butter, unsalted*	Unsalted butter	7	1 square	7	1 square
	BETWEEN MEAL FEEDING 3 P M				
Milk with protein supplement	Milk	240	½ pint	240	½ pint
	Dried skim milk†			30	4 tablespoons

* Note limitations listed in Table 80 † May use protein hydrolysate

fluids by mouth, the difficulty is such that a state of dehydration and semi starvation may result

Some years ago, such a patient was in my care Eating was difficult and she refused meat of any sort Through the help of Sister Mary Victor, head dietitian at St Marys Hospital, Rochester, Minnesota, the patient was given a meat-free liquid and semisolid diet containing 100 gm of protein daily This allowed maintenance of an adequate state of nutrition and hydration until the edema had subsided sufficiently to allow return to a routine diet I am indebted to Sister Mary Victor for permission to reprint the formula for this diet (Tables 106 and 107), which contains 99 gm of protein, 2,745 calories

TABLE 106 —HIGH CARBOHYDRATE, HIGH PROTEIN, LOW FAT DIET WITHOUT MEAT OR MEAT EXTRACTIVES*

Approximate Values

Carbohydrate	495 gm	Calories	2 745
Protein	99 gm	Fluids	1 400 cc
Fat	41 gm	Sodium	2 gm

Food Allowance, Per Day

Food	*Amount gm*	*Approximate measure*
Bread		
Whole wheat or graham	100	4 slices
Cereal	20	1 serving
Butter	15	1½ squares
Concentrated sweets		
Jelly or jam	60	4 tablespoons
Sugar—for lemonade	150	10 tablespoons
Sugar—for meals	30	2 tablespoons
Fruit		
10% fruit (orange juice)	100	1 small glass
25% fruit (canned fruit)	300	3 large servings
Lemon juice	100	Juice of 2 lemons
Protein foods		
Cottage cheese	60	1 serving
Egg whites	60	2
Eggs	200	4
Milk skimmed	960	4 glasses
Vegetables		
3% vegetables	200	2 servings
6% or 15% vegetables	200	2 servings
Potato or 20% vegetables	200	2 servings

* Tea and coffee, like other salt free fluids, are not limited in quantity

and 1,400 cc of fluid daily It should be noted, however, that it contains 2 0 gm of sodium because of the high content of egg albumin It should be observed also that, like the Borst and Bull diets already described, *it is not* altogether palatable or practical for use over long periods but should be looked on as a useful, temporary diet The low content of fat makes it inadequate with regard to fat-soluble vitamins This may be remedied by use of halibut liver oil (haliver oil) In addition, the diet should be supplemented with one of the vitamin concentrates The content of fat in the diet may be increased by the addition of salt free butter The content of protein may

be increased by adding more egg whites, which can be incorporated in many different ways The large amounts of egg whites, however would make such a diet impractical for use at home One wonders what the housewife would do with a dozen egg yolks every day!

TABLE 107 —SUGGESTED MENU FOR HIGH CARBOHYDRATE HIGH PROTEIN LOW FAT DIET WITHOUT MEAT OR MEAT EXTRACTIVES*

Breakfast	
Orange juice	1 small glass
25% fruit	1 large serving
Eggs	2
Toast	2 slices
Butter	½ square
Jelly jam or marmalade	1 rounded tablespoon
Skimmed milk	1 glass
Cereal	1 serving
Sugar	2 teaspoons
Noon Meal	
Potato or substitute	1 serving
Cottage cheese	Approximately 60 gm
Vegetables	1 serving
Bread	1 slice
Butter	½ square
Salad (with vinegar or lemon juice)	1 serving
Jelly jam or marmalade	1 rounded tablespoon
Dessert (canned fruit)	1 serving
Skimmed milk	1 glass
Sugar	2 teaspoons
Evening Meal	
Same plan as the noon meal except that 2 eggs are included in place of the cottage cheese	
Between Meal Nourishments	
10 00 A M and 3 00 P M	Albuminized lemonade (with 1 egg white juice of 1 lemon and 5 tablespoons of sugar) 1 glass
8 00 P M	Skimmed milk 1 glass

* All foods are to be cooked without added salt Only fresh or frozen vegetables should be used Dry cereals permitted include only Puffed Wheat Puffed Rice and Shredded Wheat

RESTRICTION OF SALT

Studies and observations during the past few years some of which have been alluded to previously, have indicated that sharp restriction of salt is necessary in the dietary management of renal disease only in the presence of edema As is true of a patient suffering from congestive cardiac failure, the kidneys of a nephrotic patient are often unable to excrete salt in a normal manner the water-binding effect of excessive amounts of sodium stored in the tissues tends to decrease the amount of water eliminated in the urine and to increase the amount of water stored in the tissues Hence diets restricted in sodium are of value in the treatment of nephrotic edema

TABLE 108 —DIETARY PATTERN AND SAMPLE MENU FOR RESTRICTED SODIUM DIETS IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

		Diets Using			
		Sodium, 0 4 gm Protein, 40 gm		*Sodium, 0 5 gm Protein, 70 gm*	
Dietary pattern	*Sample menu*	*Weight gm*	*Approximate measure*	*Weight, gm*	*Approximate measure*
	BREAKFAST				
Fruit*	Grapefruit	100	½ medium	100	½ medium
Cereal, unsalted	Unsalted cereal	15 (dry)	½ cup (cooked)	15 (dry)	½ cup (cooked)
Egg	Soft-cooked egg			50	1
Bread, unsalted*	Unsalted toast	25	1 slice	25	1 slice
Butter, unsalted*	Unsalted butter	14	2 squares	7	1 square
Beverage*	Coffee		1 cup		1 cup
Cream	Cream, 20%	75	⅓ cup	75	⅓ cup
Sugar	Sugar	15	1 tablespoon	15	1 tablespoon
Jelly*	Jelly	20	1 rounded tea spoon	20	1 rounded tea-spoon
	DINNER				
Soup, unsalted	Unsalted cream of potato soup	100	½ cup		
Meat, unsalted*	Unsalted roast beef			60	2 ounces
Potato unsalted*	Unsalted mashed potato with unsalted butter	100	½ cup	100	½ cup
Vegetable, unsalted*	Unsalted new cabbage with unsalted butter	75	½ cup	75	½ cup

Salad*	Sliced tomato	75	½ medium	75	½ medium
Salad dressing unsalted*	Unsalted mayonnaise	15	1 tablespoon	15	1 tablespoon
Fruit*	Sliced orange	100	1 medium	100	1 medium
Beverage	Milk	120	¼ pint	240	½ pint
Bread unsalted*	Unsalted bread	25	1 slice	25	1 slice
Butter unsalted*	Unsalted butter	14	2 squares	7	1 square
Jelly*	Jelly	20	1 rounded tea spoon		
Fruit juice	Pineapple juice	200	1 cup scant		
Sugar	Sugar	15	1 tablespoon		
	SUPPER				
Meat or substitute unsalted*	Unsalted cold beef			60	2 ounces
	Poached egg	50	1		
Potato or substitute unsalted*	Baked potato with unsalted butter	100	1 medium	100	1 medium
Vegetable unsalted*	Unsalted buttered green beans	75	½ cup	75	½ cup
Salad*	Celery and carrot sticks	60	3 to 4 of each	60	3 to 4 of each
Fruit*	Sliced banana	100	1 medium	100	1 medium
Beverage	Milk	240	½ pint	240	½ pint
Bread unsalted*	Unsalted bread	25	1 slice	25	1 slice
Butter unsalted*	Unsalted butter	14	2 squares	7	1 square
Jelly*	Jelly	20	1 rounded tea spoon		
Cream	Cream, 20%			50	3 tablespoons
Sugar	Sugar			15	1 tablespoon

* Note limitations listed in Table 80

The 2 0-gm sodium diet provides for approximately 5 gm of salt daily, and the foods in this diet are cooked with the amount of sodium chloride necessary for seasoning but no salt is served on the tray or at the table (Tables 96, 97 and 109) The restricted sodium diets provide for 0 1 to 0 8 gm of sodium (1 1 to 2 0 gm of salt) daily, as contrasted to a normal diet, which contains approximately 4 gm of sodium (8 to 10 gm of salt) these restricted diets provide 40 to 130 gm of protein daily (Tables 94 95, 96 and 105) The extremely low-sodium diet (Tables 109, 110 and 111) is a weighed diet providing approximately 70 gm of protein and 0 2 gm of sodium (0 5 gm of salt) Although it has been designed for use primarily in the hospital under close supervision, patients also may be instructed to continue its use at home under the care of a physician

TABLE 109 —APPROXIMATE COMPOSITION OF 0 2 GM SODIUM DIET*

	Amount		*Amount*
Protein	70 gm	Potassium[4]	4 1 gm.
Fat	95 gm	Vitamin A	11,800 I U
Carbohydrate	270 gm	Thiamine	1 2 mg
Calories	2 240	Riboflavin	1 2 mg
Calcium	900 mg	Niacin	13 mg
Iron	14 mg	Ascorbic acid	270 mg
Sodium[4]	0 2 gm	Water†	1,640 cc

* This diet is slightly below the recommended dietary allowances of the National Research Council in calcium and riboflavin To compensate for the deficiencies in vitamins and minerals supplemental calcium and a half vitamin supplement may be prescribed

† Exclusive of that in tea and coffee

Although a diet restricted to 0 5 gm of sodium (1 3 gm of salt) daily, in my experience, is adequate for the treatment of nephrotic edema in most cases, occasionally one may encounter a patient whose edema is refractory to such a diet and in whom it may be necessary to reduce further the content of sodium in the diet to 0 2 gm (0 5 gm of salt) daily in order to obtain satisfactory diuresis, despite the use of adjunctive diuretic measures As already noted, if such a diet is employed, the daily allowance of protein cannot exceed 70 gm

It should be observed that a definite relationship exists between the content of protein in a diet and the degree of restriction of sodium attainable All high protein diets will of necessity contain more sodium than is found in low-protein diets The amount of milk meat and eggs, which is restricted in the diets providing up to 70 gm of protein primarily because of their content of sodium, must be increased if a greater intake of protein is desired

When indications are present for restriction of salt in the diet of patients suffering from renal disease, either acute or chronic, the sodium ion is usually the one to be incriminated However, there is a relatively small group of patients in whom a decreased intake of salt is indicated because of the desirability of restricting the chloride ion It has been shown by

TABLE 110.—FOODS INCLUDED AND EXCLUDED IN THE 0.2 GM. SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Type of food	*Included*	*Excluded*
Beverage	Cereal beverage, coffee, dialyzed milk 1 pint daily, tea	Untreated milk, soft water, carbonated beverages
Bread	Bread made without baking powder, baking soda, salt or eggs	Bread or crackers made with baking powder, baking soda, eggs or salt, pancakes, waffles
Cereal	Cooked cereals prepared without salt except those excluded, Puffed Rice, Puffed Wheat, Shredded Wheat	Quick cooking Farina, dry prepared cereals except those included
Dessert	Gelatin desserts made with plain gelatin and foods allowed, unsalted pie from fruit allowed	Desserts made with eggs, untreated milk, baking powder, baking soda or salt, commercial gelatin desserts, commercial ice cream, rennet desserts
Fat	Unsalted butter, unsalted salad dressing without egg white, salad oil, unsalted shortening	Bacon fat, salted butter, salted margarine, salad dressing made with salt and egg white
Fruit	Any fruit juice, canned, cooked or raw fruit	Dried fruit containing sodium benzoate
Meat, egg or cheese	Four ounces daily of any meat or fowl prepared without salt, fish prepared without salt except those excluded, oysters, except frozen heart, liver	Salted or smoked meats, fish or fowl, salted canned meats, fish or fowl, frozen fillets of fish except whitefish, pike and lake trout, shellfish except oysters, glandular meat except liver and heart, eggs, all cheeses
Potato or substitute	Potato, macaroni, noodles, rice, spaghetti, all prepared without salt	Fried potato, potato chips, hominy
Soup	Unsalted soup made from dialyzed milk and vegetables	Any other
Sweets	Pure sugar candy, honey, jam, jelly or marmalade made without sodium benzoate, white sugar	Candy except that included, molasses, sirups, brown sugar
Vegetable	Any canned, cooked or raw vegetables or juice prepared without salt except those excluded	Vegetables prepared with salt, frozen corn, lima beans and peas and mixture of frozen vegetables containing corn, lima beans or peas, beets, beet greens, celery, chard, dandelion greens, kale, spinach
Miscellaneous	Chocolate, cocoa, herbs, spices and vinegar in moderation, unsalted nuts, unsalted peanut butter, unsalted popcorn	Catsup, chili sauce, horse-radish, gravy, prepared mustard, olives, salted peanut butter, salted pickles, relishes, salted nuts, salted popcorn, white sauce, salt, chemically softened water

TABLE 111 —DIETARY PATTERN AND SAMPLE MENU IN THE 0 2 GM SODIUM DIET IN THE DIETARY PROGRAM OF CARDIOVASCULAR RENAL DISEASE

Dietary pattern	*Sample menu*	*Weight, gm*	*Approximate measure*
	BREAKFAST		
Fruit*	Grapefruit	100	½ medium
Fruit juice*	Pineapple juice	200	1 cup, scant
Cereal unsalted*	Unsalted whole-grain cereal	15 (dry)	½ cup (cooked)
Bread, unsalted*	Unsalted toast	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square
Coffee	Coffee		1 cup
Dialyzed milk†	Dialyzed milk	240	½ pint
Sugar	Sugar	15	1 tablespoon
Jelly*	Jelly	20	1 rounded teaspoon
	DINNER		
Meat unsalted*	Unsalted roast beef	60	2 ounces
Potato or substitute*	Unsalted potato	100	½ cup
Vegetable, unsalted*	Unsalted buttered new cabbage	75	½ cup
Salad*	Sliced tomato	75	½ medium
Salad dressing*	Unsalted mayonnaise	15	1 tablespoon
Fruit*	Sliced orange	100	1 medium
Fruit juice*	Grapefruit juice	200	1 cup, scant
Bread, unsalted*	Unsalted bread	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square
Jelly*	Jelly	20	1 rounded teaspoon
	SUPPER		
Meat, unsalted*	Unsalted cold sliced beef	60	2 ounces
Potato or substitute*	Baked potato with unsalted butter	100	1 medium
Vegetable unsalted*	Unsalted buttered green beans	75	½ cup
Salad*	Carrot sticks	60	4 sticks
Dessert*	Sliced banana	100	1 medium
Dialyzed milk†	Dialyzed milk	240	½ pint
Bread unsalted*	Unsalted bread	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square
Jelly*	Jelly	20	1 rounded teaspoon

* Note limitations listed in Table 95

† The dialyzed milk used is made from dialyzed milk powder (Lonalac Mead Johnson & Evansville Indiana) 30 gm of powder is mixed in enough water to make 240 cc

numerous investigators that after excision of the urinary bladder and transplantation of the distal ends of both ureters into the sigmoid, between 80 and 90 per cent of such patients experience some degree of hyperchloremic acidosis, with increased values for chloride in the blood and depletion of the bicarbonate reserve. These changes have been ascribed in some patients to inability of the kidney adequately to excrete chloride in excessive amounts, whereas in the majority of patients it is considered to be due to reabsorption of chloride from the urine contained in the sigmoid.

TABLE 112.—LOW CHLORIDE DIET

Approximate Values

Protein	75 gm	Sodium	1.6 gm
Fat	110 gm	Chlorine	2.2 gm
Carbohydrate	260 gm	Vitamin A	5,000 I.U.
Calories	2,300	Thiamine	1.2 mg
Calcium	900 mg	Riboflavin	1.9 mg
Iron	13 mg	Niacin	14 mg
		Ascorbic acid	240 mg

This is an adequate diet according to the recommended allowances of the National Research Council.

Type of food	*Included*	*Excluded*
Beverage	Coffee, tea, cereal beverage, carbonated beverage, milk (whole or skimmed)	None
Bread	Enriched or whole grain (not more than 4 slices daily)	Crackers
Cereal	Salt-free enriched or whole grain (Puffed Rice, Puffed Wheat, Shredded Wheat)	Salted cereals
Dessert	Gelatin dessert, unsalted cake, cookies, pie, puddings made from milk allowance	Desserts made with salt
Fat	Butter, mayonnaise, margarine, vegetable oil, cream (¼ cup), not more than 3 tablespoons of butter	Bacon fat
Fruit	Fresh, cooked, canned or dried fruit	Dates, figs and bananas
Meat, egg or cheese	Beef, veal, lamb, liver, fish or fowl cooked without salt	Bacon, ham, cheese, shellfish, brains, salt-water fish
Potato or substitute	Potato, noodles, macaroni, spaghetti, rice cooked without salt	Potato chips
Salad	Fruit or vegetable made from foods allowed	
Soup	Unsalted, made from foods and milk allowed	Salted soups
Sweets	Sugar, sirup, candy made without salt or molasses	Salted candy, molasses
Salad dressing*	None unless substituted for butter	Those containing cheese, pickle or olives
Vegetable	Fresh, cooked or canned vegetables without salt	Celery, green cabbage, all greens except lettuce
Miscellaneous	Sodium bicarbonate (20 gm.), baking powder, spices, unsalted nuts, peanut butter, yeast	Salt, condiments, olives, pickles, coconut, catsup, gravies

* One tablespoon of butter equals 1 tablespoon of salad dressing.

TABLE 113 —LOW CHLORIDE DIET

Food Allowance Per Day

Food	*Approximate measure*
Beverage	
Milk	2 glasses (1 pint including that used in cooking)
Other salt-free fluids not restricted	
Meat	2 servings (4 ounces)
Eggs	1—no salt
Fruit or juice	5 servings (2½ cups)
Vegetables	3 to 4 servings (1½ to 2 cups)
Potato or substitute	2 servings (1 cup)
Butter	4 squares (3 tablespoons)
Cream	½ cup
Cereals	1 serving (½ cup)
Bread	4 slices
Soup	2 servings (1 cup)

Suggested Menu

Breakfast	
Fruit—orange juice	1 small glass
Cereal (salt-free oatmeal)	
Eggs (salt-free)	1
Bread (plain or toasted)	2 slices
Butter	2 squares
Cream	½ cup
Beverage	
Jelly	
Sugar	
Dinner	
Meat (salt free roast beef)	
Potato (salt-free mashed potato)	
Vegetable (salt-free carrots)	
Salad (head lettuce)	
Bread	1 slice
Butter	1 square
Dessert (salt-free vanilla pudding)	
Milk	½ glass
Supper	
Meat (salt-free chicken)	
Potato (baked)	
Vegetable (salt-free peas)	
Salad (salt-free tomato)	
Bread	1 slice
Butter	1 square
Dessert (fruit)	
Milk	1 glass

The clinical manifestations of this syndrome are rather characteristic and have been described in detail elsewhere[10] We have found a practical solution to this problem to be dietary in nature Use of a routine sodium poor diet (Tables 94 95 and 105) with addition of supplemental sodium bicarbonate in doses ranging from 2 to 4 gm (30 to 60 gr) daily to compensate for the deficiency of sodium in the diet, has been sufficient to correct the hyperchloremia and acidosis Once a normal balance of electro

lytes in the blood has been restored, a more liberal diet, containing 1 6 gm of sodium and 2 2 gm of chlorine daily (Tables 112 and 113) has been found to be entirely adequate to keep the condition under control

DEPRIVATION OF SALT

Any diet in which the amount of salt is drastically restricted presents the problem of possible harmful effects to the patient that may result from a deficiency of sodium or chloride particularly if a defect is present in the resorptive function of the renal tubules, which will prevent adequate conservation of salt The clinician who employs such a regimen must be constantly on the alert in evaluating complaints of weakness, lassitude, anorexia nausea and vomiting, mental confusion abdominal cramps and aching in skeletal muscles as possible indications of impending disaster in the form of depletion of salt [11] Patients receiving such diets must be kept under frequent observation particularly in warm weather when excessive amounts of salt may be lost through perspiration

SUBSTITUTES FOR SALT

For some patients a diet restricted in salt will be enhanced by use of a substitute for salt However commercial substitutes for salt available at present leave much to be desired in serving the purpose for which they are intended, namely rendering the diet more attractive and palatable to the patient Most of these substitutes contain principally either potassium chloride or ammonium chloride or both when used in small amounts these preparations are safe for most patients who have renal disease [1] However no suitable substitute for salt is available at present for patients receiving a low chloride diet because of hyperchloremic acidosis

FLUID ALLOWANCE

No indication exists for restriction of salt-free fluids for patients who have renal disease On the contrary, such patients should be encouraged to take liberal quantities of fluids (2 000 to 3 000 cc daily) In the presence of protracted nausea and vomiting parenteral administration of fluid may be necessary to prevent serious dehydration Such treatment, however must be carried on judiciously and the amount of fluid administered should not exceed in volume the amount lost from the body in urine feces and vomitus and that lost through perspiration and respiration

SUPPLEMENTATION OF VITAMINS

With the exceptions of the 70 gm protein diet already described (Table 101) and the diet containing 40 gm of protein diets used for the treatment of renal disease are entirely adequate in content of vitamins When supplemental vitamins are added to these diets they should be in the form of pharmaceutical preparations, tablets or capsules

Patients receiving fluid intravenously over a protracted period should be given fluids fortified by a vitamin preparation for parenteral administration

COMMENT

Unfortunately most of the conditions included in the field of renal disease with few exceptions, are not amenable to cure, and, therefore, control must be the prime objective in any program of treatment This implies on the part of the patient not temporary observance of a particular diet but faithful and meticulous adherence to a restricted dietary regimen for a long period Primarily, the success or failure of a well-planned dietary program requires interested and wholehearted co-operation on the part of the patient, but the physician has the responsibility of ordering the proper diet and encouraging the patient in the observance of its details His is the duty of explaining clearly to the patient the rationale of the diet and the reasons for strict adherence to it Diets used in the treatment of renal disease are limited in variety and are likely to be unpalatable to the patient Considerable ingenuity and imagination will be required to devise menus that will be as attractive and as palatable as possible and yet remain within the restrictions imposed

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Chapter 25

Nutrition in Urologic Diseases

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and

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UROLITHIASIS

The intelligent management of urolithiasis must include an evaluation of the etiologic factors in the formation of stones the chemical analysis of calculi, and the different methods of controlling and preventing their growth The factors, direct or indirect, which play a part in the genesis of urinary calculi are many and include geographic and climatic influences, age and sex, race, heredity urinary tract infection urostasis, dietary deficiencies derangements of calcium and phosphorus metabolism derangements of intermediary metabolism (as in gout) urinary crystalloid colloidal imbalance, and, finally, predisposing local lesions in the tip of the renal pyramid (Randall s plaques)

Incidence and Composition of Urinary Calculi —Renal calculi occur with almost equal frequency in both sexes Bladder calculi, however, are far more common in the male because of the additional factor of vesical orifice obstruction This disparity makes the incidence of urolithiasis in the male twice that in the female

All urinary tract calculi are composed of an organic matrix, a mucopolysaccharide—muco protein complex, and crystalloids This matrix comprises only about 2½ per cent by weight of most calculi However, it is spread throughout the entire calculus in a sort of structure or framework with both fibrillar and amorphorus elements seen on microscopic examination Histochemically matrix is composed of a combination of mucoprotein (PAS positive) and muco-polysaccharide (meta chromatic with toluidine blue) Galactose and hexosamine are the major components of the carbohydrate

The crystalline constituents of human urinary calculi are calcium oxalate monohydrate calcium oxalate dihydrate mangesium ammonium phosphate hexahydrate, apatite calcium hydrogen phosphate dihydrate uric acid cystine, and urates Apatite is the principal single complex substance present in calculi reported as showing both calcium phosphate and carbonate by chemical analysis Calcium carbonate has not been found in calculi as their sole constituent

Crystallographic analysis of 2000 human urinary calculi demonstrated that approximately 30 per cent were composed of calcium oxalate 40 per cent of calcium oxalate and apatite, 15 per cent of magnesium ammonium

phosphate alone or mixed with apatite or with apatite and calcium oxalate, 4 per cent of apatite, 5 per cent of uric acid, and 2 per cent of cystine Only one pure urate stone was found

Formation of Urinary Calculi *General Considerations* —Significant quantities of various organic substances are present in human urine in collidal form Among these are substances similar to the organic matrix (a mucoprotein muco-polysaccharide complex) common to all urinary tract calculi This material is of unknown origin Boyce *et al*, believe that the condensation of these specific molecules is the essential phase in calculus formation The subsequent growth of a formed calculus depends upon the deposition of additional matrix Deposition of crystals into the matrix material is governed by those principles of physical chemistry which control the formation of crystals from complex solutions

The above seems an oversimplification of the process of stone formation It is more probable that calculi fall in two groups from the standpoint of genesis– concretionary and sedimentary Concretionary calculi have radial striations and undergo a type of growth known as spherulitic This type of formation is commonly seen in the mineral world and appears to be based upon the purely physical chemical laws It is probable that even though matrix is found in these stones that it plays only a small role in the formation of them Sedimentary stones do not have radial striation, contain a larger amount of matrix and probably depend upon stone matrix for both their initiation and subsequent growth

Butt and his group felt that calculus formation rsulted because of a lack of "protective colloids' in the urine These protective colloids were supposed to coat microcrystalline aggregates or collections of hydrophobic (matrix?) colloid in the urine and prevent agglomeration of these substances with subsequent stone formation He attempted to increase the protective colloid in the urine by the subcutaneous administration of hyaluronidase This enzyme acted upon the ground substance of connective tissue supposedly releasing polymers of hyaluronate with appeared in the urine and acted as the protective colloid Studies on urinary surface tension and ultramicroscopic studies in some cases in which a beneficial result was obtained showed changes consistent with this hypothesis

The urine is normally supersaturated from 2 to 4 times with its crystalloid elements because of (1) the action of the protective urinary colloids, (2) the formation of weakly bound soluble complexes composed of the crystalline components of calculi and citrates, glucuronides, amino acids magnesium etc, (3) the action of the salts of strong electrolytes (*e g* sodium chloride), which usually increase the solubility of the salts of weak electrolytes (*e g* calcium phosphate) when both are present in the urine This occurs only if the strong electrolyte contains ions which are not common to the weak electrolyte

Some believe urinary calculi develop and grow when urinary crystalloids precipitate from supersaturated solutions in urine to either form a "stone nucleus" directly (on which the precipitating crystalloids can be further deposited) or when this urinary sediment deposits itself on a calcium (Randall's) plaque at the tip of the renal pyramid These plaques are initially

subepithelial They may act as "stone nuclei when the overlying mucous membrane becomes eroded

Precipitations of urinary crystalloids occur when the limit of supersaturation is exceeded, either because of increased concentration of the crystalloids or because of a derangement of urinary solubility factors Increased concentration of crystalloids may be due to insufficient urine volume or hyperexcretion

Two conditions can occur within the urinary tract which frequently accelerate the growth of a calculus (1) urinary stasis, and (2) urinary infection Urinary stasis gives more time for the urinary salts to precipitate It also increases the incidence of urinary tract infection and makes extremely difficult the eradication of such infections Infection with urea splitting organisms (proteus bacillus and certain strains of B coli and staphylococci) renders the urine alkaline Urea is hydrolyzed, producing ammonium carbonate, which eventually releases free ammonia An alkaline urine favors the precipitation of ammonium magnesium phosphate hexahydrate and apatite calculi Such stones are almost always considered to be secondary to infection

Geographic and Climatic Factors —In certain areas of the world where the inhabitants usually subsist on an improperly balanced diet, the incidence of urinary calculi is very high Such stone areas" have been reported in China India and in Turkey and Thailand In England and France during the last century urinary calculous disease occurred chiefly in childhood (mainly in the lower urinary tract) At the present time however the disease is predominantly one of adult life and of the upper urinary tract The elimination of deficiencies in the daily dietary in these countries apparently has brought about the changes of incidence and situation in calculous disease Deficiency of vitamin A of animal origin and a deficiency of absorbable calcium in the diet are thought to have been demonstrated as the important faults

If fluid intake is not proportionately increased, the excessive sweating which occurs in hot climates increases the concentration of the urinary crystalloids and thus favors their precipitation In this respect, it is noteworthy that in the United States the incidence of urinary calculi is greatest in southern California and in southern Florida

Avitaminosis A —Experimental Data —In addition to the clinical observations in the various stone areas there are experimental data to establish a relationship between stone formation in animals and an improperly balanced diet Osborne, Mendel and Ferry in 1917 found 87 cases of calculi in 857 necropsies on rats which had been 'without an adequate source of fat-soluble vitamin for some time' Prolonged vitamin A deficiency produces keratinization of the urinary tract In such a condition there is sufficient irritation to produce fibrin and mucin as a framework for the deposition of sediment and subsequent formation of stones Steiner and his associates have been able to produce ureteral and renal calculi in guinea pigs by means of a ration deficient in vitamin A

It is important to remember, however that a lack of vitamin A has frequently failed to produce stone in animals Furthermore calculi frequently occur in the urinary tracts of cattle and sheep which receive

an abundance of vitamin A from alfalfa and green pasturage We must conclude, therefore, that vitamin A deficiency is but one factor in the experimental formation of urinary stone

Avitaminosis A —Clinical Considerations —Even in the so-called "stone areas" of the United States there is no clinical evidence of widespread vitamin A deficiency, nor have actual stone cases been proved clinically to be suffering from avitaminosis A Jewett, Sloan and Strong have determined that there is no "subclinical" evidence of vitamin A deficiency in urolithiasis in man They investigated the vitamin content of the blood, the rate of dark adaptation, and the thresholds of the completely dark adapted eye in 20 patients with urolithiasis and compared them with those in 40 normal subjects The urinary tract in 78 autopsy cases with urolithiasis was also examined for evidence of epithelial metaplasia In none of these 98 cases could any evidence of vitamin A deficiency be found

In many diseased conditions, however, patients cannot maintain their body stores of essential nutrients, including vitamin A This fact may be a secondary factor in the etiology of renal calculi, but it has not been demonstrated clinically

CLINICAL CLASSIFICATION OF URINARY STONES

In order to outline the medical therapy, urinary tract calculi are grouped clinically as follows

- A Organic Stones
  - 1 Uric acid (urate) stones
  - 2 Cysteine stones
- B Calcium Stones
  - 1 Calcium oxalate (also calcium oxalate-apatite) stones
  - 2 Calcium phosphate (apatite) (also calcium phosphate magnesium ammonium phosphate) stones

Magnesium ammonium phosphate stones, with or without apatite, occur in alkaline urine, which is usually secondary to urinary infection caused by urea-splitting organisms

THE ORGANIC STONES

Uric Acid —Concretions of uric acid amount to about 6 per cent of urinary tract stones Twenty-one per cent of individuals with gout have uric acid calculi at one time or another, 25 per cent of those with gout have elevated urinary uric acid excretion levels Hyperuricemia and hyperuricosuria are sometimes found without clinical manifestations of gout Approximately one-third of individuals with uric acid calculi have elevated serum uric acid levels In one series of 11 proven cases of uric acid calculi all 11 had elevated urine uric acid excretion values

The recognized antecedents of urinary uric acid are the purines Uric acid excretion rises and falls concomitantly with the increase and decrease of purines in an otherwise normal and controlled diet Recent metabolic studies utilizing isotope tracer techniques demonstrate a considerable endogenous synthesis of purines from a variety of ingested nitrogen compounds

A significant decline in urinary uric acid excretion will occur on dietary protein restriction. This occurs even in patients who had already been on a purine restricted diet. Daily dietary protein in recurrent uric acid calculous disease should be limited to 0.3 to 0.4 gm. of high quality protein per kilogram of body weight. While a diet containing 1 gm. protein per kilogram of body weight is optimal for well-being, a diet containing 0.3 gm. *high quality* protein per kilogram of body weight will not result in a nutritional deficiency of protein.

MEDICAL THERAPY OF URIC ACID STONES

The medical therapy of uric acid stones consists of (1) greatly increasing the fluid intake (in order to decrease the urinary concentration of uric acid), (2) alkalinizing the urine (the salts of uric acid which are formed in alkaline urine are more soluble than the free acid) and, as mentioned above, (3) a low protein diet (Table 114) (to reduce the total quantity of uric acid which is excreted). Restriction of protein is especially valuable in those cases having a higher than normal urinary uric acid excretion.

TABLE 114.—LOW PROTEIN (LOW PURINE) DIET

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA—DIETARY DEPARTMENT

30 gm. Protein — Approximately 2000 Calories

The following foods may be used daily:

Only
- 1 serving cereal
- 3 slices bread
- 1 egg
- 1 oz. meat or poultry
- 2 servings potatoes or substitute
- 2 servings vegetables

Unlimited: All foods as butter or fats, cream, sugar, jelly, hard candies, fruit, coco cola, ginger ale or carbonated beverages.

Do not eat at any time the following:

Jello or gelatin, chocolate candy, milk or milk products as cheese, meat, fish and egg other than amount allowed above, cream soups, gravies, cakes or cookie, crackers, pastries or any products containing flour, nuts, sauces, ice cream and sherbets, puddings, peanut butter, marshmallows. Do not eat any products made with eggs, either whole or the whites as angel food cake or marshmallowe, etc.

As this diet is to consist of 2000 calories, it is desirable that the amounts listed in the suggested menu be eaten daily. Additional amounts may be eaten if desired of these unlimited foods.

SAMPLE MENUS

Breakfast	*Breakfast*
1 serving fruit	½ grapefruit
1 serving fruit juice	1 cup orange juice
1 serving cereal	½ cup oatmeal or ¾ cup cold
1 serving bread	1 slice bread or toast
2 squares butter	2 squares butter
1 cup beverage	1 cup coffee or tea
⅓ cup cream	⅓ cup cream
1 tbsp. sugar	1 tbsp. sugar
1 tsp. jelly	1 tsp. jelly or honey

10:00 A.M. 1 cup fruit juice plus 1 tsp. sugar

Lunch	*Lunch*
1 egg or 1 oz meat	1 scrambled egg
1 potato or extra slice bread	1 baked potato
½ cup cooked or raw vegetable	Lettuce and tomato salad
1 serving fruit	1 banana
1 serving fruit juice	1 cup grapefruit juice
1 serving bread	1 slice bread or 1 roll
2 squares butter	2 squares butter
1 tsp jelly	1 tsp jelly
1 tbsp sugar	1 tbsp sugar
Beverage	Coffee or tea

2 00 P M 1 cup fruit juice plus 1 teaspoon sugar

Dinner	*Dinner*
1 oz meat or 1 egg	1 slice roast beef
1 serving potato or substitute as noodles, spaghetti macaroni	½ cup rice
½ cup cooked vegetable	6 stalks asparagus cucumbers and onions
1 serving raw vegetable	1 slice bread
1 serving bread	2 teaspoons butter
2 teaspoons jelly	1 teaspoon jelly
1 tbsp sugar	1 tbsp sugar
1 serving fruit	1 orange
1 serving fruit juice	1 cup pineapple juice
Beverage	Coffee or tea

8 P M 1 cup fruit juice plus 1 teaspoon sugar

Alkalinizing agents are more reliable and efficacious than any dietary The low protein diet is low in acid-ash content (for practical purposes it can be considered a neutral ash diet) and has replaced the strict alkaline-ash diet as an adjuvant to urinary alkalinization

Daily determinations of urinary pH at different time intervals are necessary to judge the success of the alkalinizing program This can best be accomplished by the patient himself with indicators such as pHydrin paper or preferably, with the LaMotte pH indicator (a liquid) which is more accurate Alkalinizing agents do not maintain the urine constantly alkaline throughout twenty-four hours A satisfactory alkaline pattern however usually can be achieved by administering 3 to 4 gm of sodium citrate by mouth every six hours *around the clock*

Cystine —Cystine is a sulfur-containing amino acid and is a by-product of protein metabolism which has failed to become completely oxidized It is found normally in the urine in small quantities The tendency to excrete excessive amounts of cystine in the urine (cystinuria) often affects several members of the same family However, less than 5 per cent of cystinurics form calculi

An attempt to prevent excess urinary cystine by administering choline to effect a more perfect conversion of methionine to cystine was reported successful in 2 patients This was not confirmed in a subsequent investigation

Recent investigation seems to indicate that the basic fault in cystinuria may be the failure of a renal tubule cell transport mechanism Lysine, arginine, and cystine all appeared in the urine in excessive amounts But

there was no evidence of any error in amino acid metabolism in the body tissues in the cases studied Plasma amino acid levels were normal Thus, reabsorption of three structurally similar amino acids by the tubule cells appeared to be defective

This defect is different from that seen in Fanconi's syndrome and in hepatolenticular degeneration, in both of which a generalized gross amino-aciduria occurs

There is *no etiologic relation between cystinuria and the condition known as cystinosis in which cystine is deposited in the body tissues and in which death invariably occurs at an early age*

MEDICAL TREATMENT OF CYSTINE CALCULI

There is no conclusive evidence that in cases of cystinuria, the amount of cystine excreted in the urine can be significantly reduced by dietary measures

The solubility of cystine is greatly enhanced as the alkalinity of its solutions increases *The medical treatment of cystine calculi (and cystinuria) consists principally in alkalinizing the urine and greatly increasing the patient s fluid intake*

CALCIUM STONES

Hypercalcinuria* may play a definitive role in the formation of urinary calculi when it renders the urine too supersaturated and causes the precipitation of calcium-containing crystalloids Hypercalcinuria occurs in the following situations

1 High calcium intake
2 Hypervitaminosis D
3 Hyperparathyroidism
4 Prolonged recumbency
5 Idiopathic (renal)
6 Acidosis
7 Post-menopausal
8 Cushing s syndrome

The daily dietary calcium requirement for the average adult is 0 8 gm Greater amounts are required in pregnancy during lactation and during adolescence

Hypercalcinuria occurs in individuals who are excessive milk drinkers or in ulcer patients who ingest a large amount of cream and milk One must remember that important amounts of available calcium (up to 0 2 gm daily) may be obtained from hard drinking water

Hypervitaminosis D may result in hypercalcinuria by increasing calcium absorption from the gastrointestinal tract, thus causing an elevation of the serum calcium It also increases temporarily the phosphate excretion by the renal tubule cells

In hyperparathyroidism (due to a parathyroid adenoma or parathyroid hyperplasia) the increased secretion of parathormone acts on the kidney

* To determine whether there is an increased urinary excretion of calcium the patient should be given a low calcium diet (not exceeding 125 mgm /day) for an initial three-day period If then while remaining on this diet the urinary calcium excretion exceeds 200 mgm /day hypercalcinuria is present

to enhance the excretion of phosphorus This, in turn, leads to a low serum phosphorus and to reabsorption of calcium and phosphate from the bones Thus, hypercalcemia, hypercalcinuria and hyperphosphaturia develop As hyperparathyroidism (which is curable by surgical removal of the pathologic parathyroid tissue) is the cause of 2 to 8 per cent of all cases of renal calculi, serum calcium and serum phosphorus determinations always should be done in the routine study of renal calculosis It must be remembered that a portion of the calcium is bound to protein (the albumin fraction) and that a portion is ionized Only the ionized calcium is affected by hyperparathyroidism In the presence of a low serum protein, the total calcium level might be normal or even decreased, despite the fact that the ionized calcium level simultaneously might be normal or higher than normal Hypercalcinuria, together with a low serum phosphorus (below 3 mgm *per cent*) *and an elevated serum calcium* (*above* 10 5 *mgm per cent*), usually indicates hyperparathyroidism In these circumstances surgical exploration of parathyroid glands is advisable

TABLE 115 —HIGH CALCIUM FOODS

(Nutritional Data Wooster, H A , Jr , and Blanck F C Pittsburgh H J Heinz Co , 1950)

*Dietary Sources** (*Mg per 100 gm of Edible Portion*)

Almonds	254	Kale	225
Beans, common or kidney dry	148	Milk, fresh, whole	118
		Molasses cane	273
Broccoli	130	Mustard greens	220
Cheese	873	Olives green	101
Egg yolk	147	Soybeans whole	227
Ice cream plain	132	Turnip greens	259

* Abstracted from U S D A Misc Pub No 572

Hypercalcinuria occurs in almost all patients who are subjected to periods of prolonged recumbency Immobilization results in rarefaction of bones due to decalcification The hypercalcinuria usually begins in the first week of immobilization and continues for a period of four to eight weeks, after which the calcium excretion levels drop to normal or subnormal values

Idiopathic hypercalcinuria refers to a condition in which the hyperexcretion of calcium is due to a defect at a renal level The serum calcium is normal or low, and there is no renal acidosis Many of these patients have had a staphylococcal pyelonephritis in the past This type of hypercalcinuria was found to be present in approximately 60 per cent of cases of calcium urolithiasis studied

Acidosis may cause secondary hypercalcinuria by increasing the rate of dissolution of bone Acidosis due to various types of renal insufficiency also may cause hypercalcinuria directly, as follows (1) Either acquired damage or inherent defects in the tubule cells can cause a deficiency in the

renal mechanisms for conservation of base In these circumstances calcium, potassium, and sodium either singly or together might be excreted in excessive amounts in the urine (2) In Fanconi's syndrome there is gross amino aciduria, due to an inherent tubular fault All the renal mechanisms for the conservation of base are functioning normally and to full capacity However, calcium, potassium, and sodium are all excreted in large amounts in the urine, in combination with the amino acids

In postmenopausal states a deficiency of estrogen is present Estrogen normally stimulates the osteoblasts to lay down bone matrix, and when estrogen is deficient, osteoporosis results with hypercalcinuria supervening secondarily

In osteoporosis of Cushing's syndrome insufficient bone matrix is laid down Simultaneously, bone resorption continues, with the liberation of calcium and phosphorus which are excreted in the urine This osteoporosis is due to a hypersecretion of cortisone or cortisone-like substances which exert an antianabolic effect on protoplasm in general, including, of course, that in bone matrix

Medical Therapy of Urinary Calcium Stones —In all types of calcium stones the following clinical investigations are necessary to guide medical therapy

(1) Determination of the type of the calcium-containing calculus (*x* ray appearance, urinalysis chemical analysis preferably through crystallography)
(2) Investigation of the status of the urinary tract (correct urinary stasis and specifically treat infection if present)
(3) Determine if hypercalcemia and/or hypercalcinuria are present (correct the cause if possible)

For all types of calcium stones the following general therapy is indicated

(1) Increase of urinary volume
(2) Dietary restriction of certain components of urinary stones
(3) Acidification of the urine
(4) Administration of substances to reduce the excretion of the certain components of calculi

It should be remembered that all urinary tract calculi are composed of an organic matrix and crystalloids Matrix may be an extremely important or even necessary factor in most calculogenesis If this be true it is unfortunate, for we have, at present no adequate therapy to counteract the effect of matrix on stone formation Therefore prophylactic therapy for urinary tract calculi has usually been directed at changing the urinary concentration of the crystalline components of stones

The solubility of calcium phosphate and magnesium ammonium phosphate in urine increases as the pH values of the urine decrease The solubility of calcium oxalate in urine is relatively unaffected by changes in the pH values However, calcium oxalate calculi usually have apatite nuclei In recurrent stone formation of this type mixed calcium oxalate-

apatite stones may also occur. Acidification of the urine may inhibit this stone formation.

Acidification of the urine may be accomplished by oral administration of 2 to 3 gm. of sodium acid phosphate daily. This drug also reduces calcium excretion in the urine. Ammonium chloride and strict acid ash diets are contraindicated, as they tend to increase calcium excretion in the urine. When the urine is persistently alkaline due to the presence of urea-splitting organisms, acidification may be difficult. A vigorous endeavor to eradicate the infection by specific chemo- and antibiotic therapy must be made. Even in the face of such infection the administration of 12–15 grams of methionine daily will succeed in converting the uring to an acid pH (oxidation of the sulfur in methionine to sulfate occurs in kidney and the increased urinary sulfate renders the urine acidic). Mandelamine should be administered also as an adjuvant.

Calcium excretion in the urine may be decreased by the administration of sodium phytate, a salt of inositol hexaphosphoric acid. This substance forms relatively insoluble compounds with calcium in the gastrointestinal tract increasing fecal calcium excretion. Calcium balance is not appreciably affected, however. A dose of 9 gms. per day in the form of a 15 per cent solution of sodium phytate is recommended. Moderate catharsis may be an unpleasant side effect.

Specific Therapy for Calcium Phosphate (Apatite) and Calcium Phosphate (Apatite)-Magnesium Ammonium Phosphate Calculi.—A low calcium, low phosphorus diet (Table 102) and orally administered aluminum gels greatly reduce the number of phosphate ions in the urine. The gels limit phosphate absorption from the gastrointestinal tract by forming insoluble complexes which are eliminated in the feces. Recommended doses are 40 cc. of Amphogel® or 30 cc. of Basaljel®, after each meal and at bedtime. If this therapy is to be successful, the urinary phosphate excretion should be maintained below 300 mgm. per twenty-four hours. This must be determined by periodic urine examination. Impaired renal function and alkaline infected urine do not hamper the effectiveness of this therapy. A new, more efficacious aluminum gel, Hyalgel, when taken in doses of 30 to 40 ml. at mealtime and bedtime will reduce the urinary phosphorus excretion to 400 mgm/24 hours or below even while on a normal diet.

TABLE 116.—LOW CALCIUM LOW PHOSPHORUS DIET

(Modified from Greene, Laurence F.: *Current Therapy*, Howard F. Conn, Ed. Philadelphia, W. B. Saunders Co., 1954.)

This diet has approximately 2,326 calories and 70 gm. of protein. It meets recommended dietary allowances except for calcium and riboflavin. It contains approximately 354 mgm. of calcium and 857 mgm. of phosphorus.

Foods included

Cereal beverage, coffee, tea
Refined bread: 6 slices daily, saltines if substituted for bread
Refined cereals
Gelatin desserts made of allowed foods, fruit ices
Butter or substitute, cream, not more than ½ cup daily, cooking fats, salad oils

Cranberries, plums, canned cooked or fresh fruit or juice except those excluded no more than 3 servings daily
Meat, fish or fowl except those excluded but not more than 6 ounces daily not more than 1 egg daily including those used in cooking
Macaroni noodles, refined rice spaghetti
Broth vegetable soup made from vegetables allowed
Candy without chocolate or nuts, jam jelly sugar
Canned cooked or fresh vegetable or juice except those listed under Foods excluded no more than 2 servings daily
Pepper salt spices, vinegar

Foods excluded

Carbonated beverage chocolate flavored drinks malted beverage milk milk drinks
Whole-grain bread and crackers, hot breads
Oatmeal refined cereals enriched with calcium whole-grain cereals
Desserts made with chocolate milk egg flour cake cookies ice cream, pastries and pies, sherbets
Cream except in amount allowed salad dressings made with egg
Dried fruit bananas rhubarb
Brains, cheese clams liver lobster oysters scallops, shrimp
Barley potato whole-grain rice
Bean or pea soup cream or milk soups
Candy made with chocolate milk molasses or nuts, honey molasses syrup
Dried beans broccoli celery chard collards endive greens leaf lettuce lentils okra dried peas spinach water cress
Cream sauce gravy nuts olives peanut butter popcorn yeast

SAMPLE MENU

	Weight in gm	Approximate measure
Breakfast		
Grapefruit	200	1 small
Refined cereal	15 (dry)	½ cup (cooked)
Egg		1
White toast	50	2 slices
Butter	14	2 squares
Cream 20%	75	⅓ cup
Sugar	15	1 tablespoon
Jelly	20	1 tablespoon
Coffee		1 cup
Dinner		
Orange juice	(200 cc)	⅔ glass
Roast beef	120	4 ounces
Noodles	15 (dry)	½ cup (cooked)
Sliced tomato salad	75	½ large
French dressing	15	1 tablespoon
Canned pear	75	2 halves
White bread	50	2 slices
Butter	14	2 squares
Jelly	20	1 tablespoon
Supper		
Baked ham	60	2 ounces
Refined rice	15 (dry)	½ cup (cooked)
Carrots	75	½ cup
Canned peach	75	2 peach
White bread	50	2 slices
Butter	14	2 squares
Jelly	20	1 tablespoon

20 ZINSSER J Urol *63*, 929, 1950
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Chapter 26

A. Nutrition in Cardiovascular Disease

By Howard M. Odel

HYPERTENSION

Hypertension by itself is not a disease. Rather it is a symptom complex that may manifest itself in the course of many disorders and whose development may be based on one of several mechanisms. It may occur as a symptom in the course of such diseases as acute, subacute or chronic glomerulonephritis, pyelonephritis, lesions of the brain, notably tumors, polycystic renal disease, congenital anomalies of the kidneys, hyperthyroidism, coarctation of the aorta and tumors of the adrenal glands such as pheochromocytoma. When hypertension occurs in the course of any of these conditions, management of the secondary hypertension is directed for the most part toward diagnosis and treatment of the primary condition.

In addition to patients who have these forms of hypertension for which known causes exist, many patients suffer from well-recognized, persistent, chronic hypertensive disease. By far the most common form of this latter type of elevated blood pressure is essential hypertension, or diffuse arteriolar disease with hypertension, the cause of which is still unknown even though it was first described by Richard Bright in 1827.[1]

In the following consideration of the nutritional management of hypertension only essential hypertension will be considered. In any discussion of the present concepts of the pathogenesis of essential hypertension little can be added to the poignant paragraph of Dr. George Morris Piersol found in the first edition of Wohl's *Dietotherapy*:

> Richard Bright, as long ago as 1836, argued that the kidney was the organ most frequently at fault in the production of chronic hypertension. During the years that have elapsed since Bright's observations many theories have been advanced as to the pathogenesis of hypertension. A belief which dominated medical thought for many years was that hypertension was due primarily to overactivity of the sympathetic nervous system. It remained for Goldblatt and his associates in 1934 to establish on a firm experimental basis the role that the kidneys play in the production of this symptom. It is now quite generally agreed that in some way the kidney is implicated in the production of hypertension. The most satisfactory hypothesis is that renal ischemia initiates the development of hypertension in most instances. The work of Page, Corcoran and their associates as well as that of Harrison, Grollman and Williams and that of Houssay and Braun Menendez and others, has demonstrated that there is also a humeral (sic) mechanism responsible for the production of hypertension. It seems not unlikely, therefore, that pressor substances are liberated when kidneys

are ischemic and that these substances enter the general circulation and raise peripheral resistance by their action upon the smooth muscles of arterioles, thus initiating an elevation of blood pressure. Furthermore, antipressor substances have been isolated in kidney extracts. Whether essential hypertension is due to failure on the part of the kidney, the hemodynamics of which have been altered, to produce an adequate amount of antipressor substance or whether the fault lies in excessive production of the pressor factor, is still open to conjecture. The final conclusion must rest upon further experimental studies. Even though the present evidence strongly points to a humeral (*sic*) abnormality as the basis for hypertension, extensive clinical observation leaves no doubt that hyperactivity of the sympathetic nervous system is an important contributory factor in the production or, at least, the accentuation of the condition. Furthermore, a constitutional factor based upon individual susceptibility and heredity plays an important role in a large percentage of cases of essential hypertension. Such a conception of the pathogenesis of hypertension suggests that contrary to popular belief, dietetic or nutritional factors play little or no part in the production of this condition. Nevertheless, from the standpoint of its management they are deserving of careful consideration.

The scope of this presentation does not allow for a detailed description of the classification and clinical characteristics of the types of essential hypertension. In general essential hypertension is divided into four types (groups I, II, III and IV) on the basis of clinical and retinal findings, groups I and II represent respective degrees of severity of so-called benign hypertension, group III represents a transitional form, or "early malignant" hypertension, and group IV encompasses malignant hypertension. Benign hypertension usually develops insidiously and gradually, runs a prolonged or chronic course and rarely produces symptoms until the condition has existed for some time when secondary changes may occur in the heart, kidneys, central nervous system and peripheral arterioles. Little change is seen in the ocular fundi of patients who have benign hypertension except for retinal arteriolar narrowing, focal constrictions and varying degrees of arteriolar sclerosis depending on the chronicity of the disease. Malignant hypertension, as a rule, develops more suddenly, although in many instances benign hypertension of long standing suddenly may develop the characteristics and severity of the malignant type. Malignant hypertension as a rule occurs in younger patients, the blood pressure reaches extreme heights and the clinical course is punctuated by rapidly progressing symptoms of cardiac failure, renal insufficiency or cerebral vascular changes. Examination of the ocular fundi reveals, in addition to advanced arteriolar changes, hemorrhages and cotton-wool exudates and in patients who have severe malignant hypertension (group IV), papilledema in varying degrees.

Caloric Restriction.—Obesity is extremely common in patients who have essential hypertension. For this reason, the total caloric intake should be restricted in such patients. Great fluctuations in blood pressure often occur after the ingestion of large meals because of decreased efficiency of vasomotor regulation in patients who have essential hypertension. Furthermore, it is known from experience with all types of myocardial insufficiency that filling of the stomach may result in embarrassment to the

heart The heart then labors under the double load of hypertension and obesity For information in regard to calorically restricted diets applicable to hypertensive patients who are obese, the reader is referred to the chapter on Nutrition in Obesity and Undernutrition Chapter 30 As a general rule, a diet restricted to 1,000 to 1,200 calories daily will bring about desired results without harm to the patient In most cases reduction of excessive weight is not accompanied by more than a mild decrease in blood pressure, but in some cases the drop in blood pressure is notable or even striking Even when blood pressure is not lowered improvement in subjective symptoms, such as fatigue and dyspnea may be noted in a degree concomitant with the loss in weight

Although reduction of caloric intake and exercise in moderation are indicated in the treatment of obese patients who have uncomplicated hypertension, dietary restriction should not be too severe or be carried out over too prolonged a period To impose unnecessary or too drastic restrictions on patients suffering from uncomplicated early hypertension is frequently productive of more harm than good

Less frequently, hypertensive patients are greatly underweight and undernourished No evidence exists to support the thesis that hypertension is benefited by undernutrition hence in these patients it is important to restore weight and nutrition to as nearly normal levels as possible

In summary the best interest of either the overweight or underweight patient is served by the adjustment of caloric intake in such a manner as to bring the weight of the patient to a normal level

Protein —For years, sharp restriction of protein has been widely used in the treatment of essential hypertension among some members of the medical profession and laity alike This belief has been inculcated so firmly in the minds of the laity that many patients who have hypertension literally have a phobia concerning meat and its supposedly harmful effects In fact some patients voluntarily or by a physician s order have made such drastic restriction of protein in their diets that they have experienced symptoms and signs of deprivation of protein namely weakness wasting hypoproteinemia with edema and anemia Up to the present time evidence does not exist that ingestion of protein plays any role in the production or aggravation of hypertension Therefore adequate justification is not present for rigid restriction of protein in the diet of hypertensive patients as long as the ability of the kidneys to excrete nitrogen remains adequate As is the case with all foods in the diet of hypertensive patients moderation should be exercised in the amount of protein eaten but there should be no objection to a reasonable amount of meat and the temperate use of other protein foods

Restriction of Fluid —Opinion varies with regard to the practice of restriction of fluid in hypertensive patients Physicians who are of the opinion that hypertension may be caused or aggravated by faulty elimination have encouraged patients to ingest large quantities of water and other fluids Fortunately the number who share this belief is small for evidence shows that ingestion of extremely large quantities of fluid may contribute to further increase of blood pressure in hypertensive persons An abnormally large intake of fluid tends to increase the blood volume thereby

adding to the work of an already overtaxed myocardium Although the practice of urging abnormally large intakes of fluid is to be discouraged, there is no adequate reason for great restriction of fluid and the patient should be allowed to drink fluids at will

Restriction of Beverage —No evidence exists that alcohol as such plays any part in the causation or aggravation of hypertension consequently, the temperate use of alcoholic beverages by patients who have uncomplicated hypertension is not contraindicated However, because of the other effects of alcohol, the use of these beverages in quantities other than strictly moderate should be discouraged The use of coffee or tea in moderation is probably harmless to most patients who have essential hypertension However, their use in patients who suffer from extreme nervousness, irritability or insomnia should be sharply restricted or even prohibited

Restriction of Salt —The belief that restriction of the intake of salt is beneficial to patients who have essential hypertension, as well as other forms of cardiovascular renal disease, is not new but appears to have arisen as the result of the work of Ambard and Beaujard,[3] in the early part of the present century These investigators were the first to record the observation that deprivation of salt may result in a decrease in blood pressure in persons who have essential hypertension In 1922 Allen and Sherrill[4] found that diets sharply restricted in salt were effective in lowering the blood pressure of some hypertensive patients Like Ambard and Beaujard and others, Allen and Sherrill were of the opinion that restriction of chloride rather than of sodium was the effective feature of a low-salt regimen

The introduction by Kempner,[5] in 1944, of the rice-fruit diet constitutes one of the more recent attempts at control of essential hypertension by dietary means This diet made up solely of rice, fruit and fruit juice, gives approximately 20 gm of protein per day, it contains no protein of animal origin and gives approximately 0 2 gm of sodium per day (Tables 118 and 119) Kempner explained the beneficial results of such a program in the treatment of hypertension on the assumption that hypertension produces functional impairment of cellular elements in the kidneys because of a decreased supply of oxygen to these cells Substitution of vegetable protein for animal protein in the diet is effected on the supposition that the damaged kidney in hypertension no longer can excrete adequately all the end products of metabolism of animal protein In his early reports, Kempner[6] observed objective improvement in almost two-thirds of 500 patients, this improvement was evidenced by significant decrease in blood pressure reduction in cardiac size, reversal of abnormal electrocardiographic patterns, return to normal or near normal values for urea and other retained metabolites in the blood, and regression of characteristic hypertensive changes in the ocular fundi The diet caused loss of weight in most of his patients and in his hands did not induce negative nitrogen balance However it has been shown since this early work of Kempner that strict adherence to a rice-fruit diet for some time will induce negative nitrogen balance in some patients [7] this observation, plus the loss of weight, has led to the suggestion that the rice fruit diet is, in reality, a semistarvation diet Most of Kempner's earlier claims have been ques-

tioned by other investigators in the field Some workers doubt that the diet exerts a specific antipressor or depressor effect on the blood pressure of hypertensive patients others consider that the frequent occurrence of the salt-depletion syndrome in some patients consuming the rice-fruit diet indicates a great need for discrimination in its use Final evaluation of the rice-fruit program is not possible at this time primarily because of lack of

TABLE 118 —RICE FRUIT DIET OF KEMPNER[5]

Approximate Values

Carbohydrate	460 gm	Calories	2 000
Protein	20 gm	Sodium	0 2 gm
Fat	5 gm	Chloride	0 15 gm
Fluids	700 to 1 000 cc (no water)		

Food Allowance Per Day

Food		*Approximate measure*
Rice	Any kind may be used boiled or steamed in plain water or fruit juices without the addition of salt milk or fat	1 to 1½ cups (dry measurement uncooked)
Fruits	All fruits except avocados, bananas dates and nuts May be fresh, canned or dried if nothing but sugar has been added	4 to 5 servings (2 to 2½ cups)
Fruit juices	All fruit juices Tomato juice and vegetable juices not allowed	4 to 5 glasses
Sugar	Brown or white Part may be made into syrup	½ cup or more
Water		None except that used in cooking or preparing meals

TABLE 119 —SUGGESTED MENU FOR RICE FRUIT DIET*

Breakfast	
Grapefruit	½
Cooked rice with brown sugar	2 servings (1 cup)
Orange juice with sugar added	1 glass
Noon meal	
Cooked rice	3 servings (1½ cups)
Canned pear juice	1 glass
Dessert	
Cooked rice	1 serving (½ cup)
Sliced canned or fresh peach	1
Evening meal	
Cooked rice with sugar	3 servings (1½ cups)
Pineapple juice	1 glass
Sliced orange	1
Between meal nourishments	
Two glasses of fruit juice are to be taken during the day	

* Vitamin and mineral supplements should be prescribed so that the patient receives the following daily as minimal doses vitamin A 5 000 units vitamin D, 1 000 units thiamine chloride 5 mg riboflavin 5 mg niacin amide, 25 mg calcium pantothenate, 2 mg, ferrous sulphate, 0 6 gm

fundamental knowledge regarding its effect on the human organism It will result in a decrease of blood pressure in some hypertensive patients However, it does not, in all probability, provide the clinician with a means of treating the cause or causes of essential hypertension Rather, it provides a method of relieving symptoms attributable to hypertension and of temporarily decreasing blood pressure in some patients However, it is dangerous to some patients and curative to none

While Kempner has ascribed the therapeutic effect of the rice-fruit diet to the nature and amount of protein allowed, others have contended that drastic restriction of salt is the responsible factor The exact relationship between sodium chloride and the genesis of essential hypertension is, at the present time, unknown It would appear to be extremely complex, any attempt to analyze it into component parts would necessitate specific knowledge regarding the relation of the kidneys to hypertension, the relation of the adrenal glands to salt balance and the relation of other unknown influences to the adrenal glands themselves

Grollman and his associates[8] observed a striking decrease in the blood pressure of 6 patients who had essential hypertension and who were treated with a diet that was more liberal than the rice-fruit diet but that provided less than 0 5 gm of sodium (1 3 gm of sodium chloride) daily They considered the basis for the success of this form of treatment to be the drastic *restriction of sodium chloride in the diet* and stated not only that moderate restriction of sodium fails to influence blood pressure appreciably, but also that the employment of moderate rather than drastic restriction of sodium in the diet may account for many of the therapeutic failures reported

TABLE 120 —APPROXIMATE COMPOSITION OF DIETS CONTAINING VARIOUS AMOUNTS OF SODIUM

		Amount of sodium provided, gm		
Constituent	*Unit*	*0 2**	*0 5*	*2 0*
Protein	gm	70	70	70
Fat	gm	95	125	125
Carbohydrate	gm	270	210	200
Calories		2,240	2,240	2 190
Calcium	mg	900	990	1 020
Iron	mg	14	13	13
Sodium[9]	gm	0 2	0 5	2 0
Potassium[9]	mg	4 100	3 470	3 420
Vitamin A	I U	11,800	9 600	9 400
Thiamine	mg	1 2	1 1	1 1
Riboflavin	mg	1 2	1 8	1 9
Niacin	mg	13	13	13
Ascorbic acid	mg	270	185	130
Water†	cc	1 640	1,420	1 340

* This diet is slightly below the recommended dietary allowances of the National Research Council in riboflavin *To compensate for the deficiency in vitamins a half vitamin supplement may be prescribed*

† Exclusive of that in tea and coffee

TABLE 121 —FOODS INCLUDED AND EXCLUDED IN THE 0 2 GM SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Type of food	*Foods included*	*Foods excluded*
Beverage	Cereal beverage coffee dialyzed milk 1 pint daily, tea	Untreated milk soft water carbonated beverages
Bread	Bread made without baking powder baking soda salt or eggs	Bread or crackers made with baking powder baking soda eggs or salt, pancakes, waffles
Cereal	Cooked cereals prepared without salt except those excluded, puffed Rice, Puffed Wheat, Shredded Wheat	Quick cooking Farina, dry prepared cereals except those included
Dessert	Gelatin desserts made with plain gelatin and foods allowed unsalted pie from fruit allowed	Desserts made with eggs untreated milk baking powder baking soda or salt commercial gelatin desserts commercial ice cream, rennet desserts
Fat	Unsalted butter, unsalted salad dressing without egg white salad oil, unsalted shortening	Bacon fat salted butter salted margarine salad dressing made with salt and egg white
Fruit	Any fruit juice canned cooked or raw fruit except those excluded	Dried fruit containing sodium benzoate raw apples cantaloupe honeydew melon watermelon
Meat egg or cheese	Four ounces daily of any meat or fowl prepared without salt fish prepared without salt except those excluded, oysters except frozen, heart, liver	Salted or smoked meats fish or fowl salted canned meats fish or fowl, frozen fillets of fish except whitefish pike and lake trout shellfish except oysters, glandular meat except liver and heart eggs all cheeses
Potato or substitute	Potato macaroni noodles, rice spaghetti, all prepared without salt	Fried potato potato chip hominy
Soup	Unsalted soup made from dialyzed milk and vegetables	Any other
Sweets	Pure sugar candy honey jam jelly or marmalade made without sodium benzoate white sugar	Candy except that included, molasses, sirups brown sugar
Vegetable	Any canned cooked or raw vegetables or juice prepared without salt except those excluded	Vegetables prepared with salt frozen corn, lima beans and peas and mixture of frozen vegetables containing corn lima beans or peas beets beet greens celery chard dandelion greens kale spinach dried beans broccoli Brussels sprouts cabbage cauliflower cucumbers kohlrabi onions dried peas green peppers radishes, rutabagas sauerkraut turnips
Miscellaneous	Chocolate cocoa herbs spices and vinegar in moderation unsalted nuts unsalted peanut butter unsalted popcorn	Catsup chili sauce horse-radish gravy prepared mustard olives salted peanut butter salted pickles relishes salted nuts salted popcorn white sauce salt chemically softened water

fundamental knowledge regarding its effect on the human organism It will result in a decrease of blood pressure in some hypertensive patients However, it does not, in all probability, provide the clinician with a means of treating the cause or causes of essential hypertension Rather, it provides a method of relieving symptoms attributable to hypertension and of temporarily decreasing blood pressure in some patients However, it is dangerous to some patients and curative to none

While Kempner has ascribed the therapeutic effect of the rice fruit diet to the nature and amount of protein allowed, others have contended that drastic restriction of salt is the responsible factor The exact relationship between sodium chloride and the genesis of essential hypertension is, at the present time, unknown It would appear to be extremely complex, any attempt to analyze it into component parts would necessitate specific knowledge regarding the relation of the kidneys to hypertension, the relation of the adrenal glands to salt balance and the relation of other unknown influences to the adrenal glands themselves

Grollman and his associates[8] observed a striking decrease in the blood pressure of 6 patients who had essential hypertension and who were treated with a diet that was more liberal than the rice fruit diet but that provided less than 0 5 gm of sodium (1 3 gm of sodium chloride) daily They considered the basis for the success of this form of treatment to be the drastic restriction of sodium chloride in the diet and stated not only that moderate restriction of sodium fails to influence blood pressure appreciably, but also that the employment of *moderate rather than drastic restriction of sodium* in the diet may account for many of the therapeutic failures reported

TABLE 120 —APPROXIMATE COMPOSITION OF DIETS CONTAINING VARIOUS AMOUNTS OF SODIUM

		Amount of sodium provided, gm		
Constituent	*Unit*	*0 2**	*0 5*	*2 0*
Protein	gm	70	70	70
Fat	gm	95	125	125
Carbohydrate	gm	270	210	200
Calories		2,240	2 240	2 190
Calcium	mg	900	990	1,020
Iron	mg	14	13	13
Sodium[9]	gm	0 2	0 5	2 0
Potassium[9]	mg	4 100	3 470	3 420
Vitamin A	I U	11 800	9 600	9 400
Thiamine	mg	1 2	1 1	1 1
Riboflavin	mg	1 2	1 8	1 9
Niacin	mg	13	13	13
Ascorbic acid	mg	270	185	130
Water†	cc	1,640	1,420	1 340

* This diet is slightly below the recommended dietary allowances of the National Research Council in riboflavin To compensate for the deficiency in vitamins a half vitamin supplement may be prescribed

† Exclusive of that in tea and coffee

TABLE 121 —FOODS INCLUDED AND EXCLUDED IN THE 0 2 GM SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Type of food	*Foods included*	*Foods excluded*
Beverage	Cereal beverage coffee dialyzed milk 1 pint daily tea	Untreated milk soft water carbonated beverages
Bread	Bread made without baking powder baking soda, salt or eggs	Bread or crackers made with baking powder, baking soda eggs or salt, pancakes, waffles
Cereal	Cooked cereals prepared without salt except those excluded, puffed Rice, Puffed Wheat Shredded Wheat	Quick cooking Farina, dry prepared cereals except those included
Dessert	Gelatin desserts made with plain gelatin and foods allowed unsalted pie from fruit allowed	Desserts made with eggs untreated milk baking powder baking soda or salt, commercial gelatin desserts commercial ice cream, rennet desserts
Fat	Unsalted butter unsalted salad dressing without egg white salad oil unsalted shortening	Bacon fat salted butter salted margarine, salad dressing made with salt and egg white
Fruit	Any fruit juice canned, cooked or raw fruit except those excluded	Dried fruit containing sodium benzoate raw apples cantaloupe honeydew melon, water melon
Meat egg or cheese	Four ounces daily of any meat or fowl prepared without salt, fish prepared without salt except those excluded, oysters except frozen heart, liver	Salted or smoked meats fish or fowl salted canned meats fish or fowl, frozen fillets of fish, except whitefish pike and lake trout shellfish, except oysters, glandular meat except liver and heart eggs, all cheeses
Potato or substitute	Potato macaroni noodles rice spaghetti, all prepared without salt	Fried potato potato chips hominy
Soup	Unsalted soup made from dialyzed milk and vegetables	Any other
Sweets	Pure sugar candy, honey jam, jelly or marmalade made without sodium benzoate white sugar	Candy except that included molasses, sirups, brown sugar
Vegetable	Any canned cooked or raw vegetables or juice prepared without salt except those excluded	Vegetables prepared with salt frozen corn, lima beans and peas and mixture of frozen vegetables containing corn lima beans or peas beets beet greens celery chard dandelion greens kale spinach, dried beans broccoli Brussels sprouts cabbage cauliflower cucumbers kohlrabi, onions dried peas green peppers radishes, rutabagas sauer kraut turnips
Miscellaneous	Chocolate cocoa herbs spices and vinegar in moderation unsalted nuts unsalted peanut butter unsalted popcorn	Catsup chili sauce horse-radish gravy, prepared mustard, olives salted peanut butter salted pickles relishes salted nuts salted popcorn white sauce salt chemically softened water

In my experience, neither the rice-fruit diet nor a weighed low-sodium (0 2-gm) diet (Tables 120, 121 and 122) has been strikingly effective in reducing blood pressure in the majority of patients who have severe essential hypertension, other observers have reported similar results[10–14] Occasionally, I have observed a patient who had essential hypertension whose blood pressure appeared to decrease when a weighed, low-sodium diet was employed, but in general the results have not been encouraging For this reason, until recently, my colleagues and I have reserved a trial with the rice-fruit diet or drastic restriction of sodium for the group of patients suffering from severe advanced hypertensive disease who have not

TABLE 122 —DIETARY PATTERN AND SAMPLE MENU IN THE 0 2 GM SODIUM DIET IN THE DIETARY PROGRAM OF CARDIOVASCULAR RENAL DISEASE

Dietary pattern	*Sample menu*	*Wt , gm*	*Approx measure*
	Breakfast		
Fruit*	Grapefruit	100	½ medium
Fruit juice*	Pineapple juice	200	1 cup scant
Cereal unsalted*	Unsalted whole-grain cereal	15 (dry)	½ cup (cooked)
Bread, unsalted*	Unsalted toast	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square
Coffee	Coffee		1 cup
Dialyzed milk†	Dialyzed milk	240	½ pint
Sugar	Sugar	15	1 tablespoon
Jelly*	Jelly	20	1 rounded teaspoon
	Dinner		
Meat, unsalted*	Un alted roast beef	60	2 ounces
Potato or substitute*	Unsalted potato	100	½ cup
Vegetable unsalted*	Unsalted buttered carrots	75	½ cup
Salad*	Sliced tomato	75	½ medium
Salad dressing*	Unsalted mayonnaise	15	1 tablespoon
Fruit*	Sliced orange	100	1 medium
Fruit juice*	*Grapefruit juice*	200	1 cup scant
*Bread unsalted**	Unsalted bread	25	1 slice
Butter, unsalted*	Unsalted butter	7	1 square
Jelly*	Jelly	20	1 rounded teaspoon
	Supper		
Meat unsalted*	Unsalted cold sliced beef	60	2 ounces
Potato or substitute	Baked potato with unsalted butter	100	1 medium
Vegetable unsalted*	Unsalted buttered green beans	75	½ cup
Salad*	Carrot sticks	60	4 sticks
*Dessert**	Sliced banana	100	1 medium
Dialyzed milk†	Dialyzed milk	240	½ pint
Bread unsalted*	Unsalted bread	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square
Jelly*	*Jelly*	20	1 rounded teaspoon

* Note limitations listed in Table 121

† The dialyzed milk used is made from dialyzed milk powder (Lonalac Mead *Johnson & Company Evansville Indiana*), 30 gm of powder is mixed in enough water to make 240 cc

TABLE 123 —FOODS INCLUDED AND EXCLUDED IN THE 0 5-GM SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Type of food	*Foods included*	*Foods excluded*
Beverage	Carbonated beverages not more than ½ pint daily cereal beverage coffee tea milk 1 pint daily, including that used in cooking	Soft water, cultured buttermilk
Bread	Bread made without baking powder, baking soda or salt	Bread and crackers made with baking powder baking soda or salt, pancakes waffles
Cereal	Cooked cereals prepared without salt Puffed Rice Puffed Wheat Shredded Wheat	Dry prepared cereals except those included
Dessert	Custard or ice cream made from milk and egg allowance, gelatin desserts made with plain gelatin and foods allowed unsalted fruit pie puddings made from foods allowed, desserts made without salt baking powder baking soda or egg white	Desserts prepared with salt, baking powder, baking soda or egg white commercial gelatin desserts commercial ice cream rennet desserts
Fat	Unsalted butter cream ½ cup daily salad oil unsalted salad dressing vegetable fat unsalted shortening	Salted butter bacon fat salted salad dressing salted margarine
Fruit	Any juice canned cooked or raw fruit except those excluded	Dried fruit containing sodium benzoate raw apples cantaloupe honeydew melon watermelon
Meat egg or cheese	Meat or fowl in allowed amounts prepared without salt fish except those excluded oysters except frozen heart liver eggs in allowed amounts	Salted or smoked meats fish or fowl, salted canned meats fish or fowl frozen fillets of fish except whitefish pike and lake trout shellfish except oysters glandular meat except liver and heart all cheeses
Potato or substitute	Potato macaroni noodles rice spaghetti	Fried potato potato chips hominy
Soup	Unsalted broth or cream soup made from milk allowance	Any other
Sweets	Pure sugar candy jam jelly or marmalade made without sodium benzoate sugar sirup honey molasses	Jam or jelly containing sodium benzoate candy except that included
Vegetable	Any canned cooked or raw vegetable or juice prepared without salt except those excluded beets beet greens celery chard dandelion greens kale and spinach no more than one serving daily	Vegetables prepared with salt frozen corn lima beans or peas and mixtures of frozen vegetables containing corn lima beans or peas dried beans broccoli Brussels sprouts cabbage cauliflower cucumbers kohlrabi onions dried peas green peppers radishes rutabagas sauerkraut turnips
Miscellaneous	Chocolate cocoa unsalted white sauce herbs spices and vinegar in moderation unsalted nuts unsalted peanut butter unsalted popcorn	Catsup chili sauce gravy horseradish mustard olives salted peanut butter salted pickle salted popcorn relishes salt salted nuts chemically softened water

responded to various medicinal means of controlling blood pressure and who have been adjudged unsuitable candidates for surgical treatment. However more recently we have noted an observation, commented on repeatedly in the literature by other workers in the field, that the effectiveness of antihypertensive drugs such as hexamethonium, hydralazine and the derivatives of Rauwolfia serpentina often is enhanced when the patient is maintained on a diet moderately restricted in sodium, in such cases, we have employed a diet containing 0 5 gm of sodium daily (Tables 123, 124 and 120) The majority of hypertensive patients treated by means of diets in which salt is severely restricted have reported definite, and in some instances, pronounced relief of symptoms, particularly head ache, tinnitus, vertigo and other distressing cerebral symptoms In gen-

TABLE 124 – DIETARY PATTERN AND SAMPLE MENU FOR 0 5-GM SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Dietary pattern	*Sample menu*	*Wt, gm*	*Approx measure*
	Breakfast		
Fruit*	Grapefruit	100	½ medium
Cereal unsalted	Unsalted cereal	15 (dry)	½ cup (cooked)
Egg	Soft-cooked egg	50	1
Bread unsalted*	Unsalted toast	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square
Beverage*	Coffee		1 cup
Cream	Cream 20%	75	⅓ cup
Sugar	Sugar	15	1 tablespoon
Jelly*	Jelly	20	1 rounded teaspoon
	Dinner		
Meat unsalted*	Unsalted roast beef	60	2 ounces
Potato unsalted*	Unsalted mashed potato with unsalted butter	100	¼ cup
Vegetable, unsalted*	Unsalted beets with unsalted butter	75	½ cup
Salad*	Sliced tomato	75	½ medium
Salad dressing unsalted*	Unsalted mayonnaise	15	1 tablespoon
Fruit*	Sliced orange	100	1 medium
Beverage	Milk	240	½ pint
Bread, unsalted*	Unsalted bread	25	1 slice
Butter, unsalted*	Unsalted butter	7	1 square
	Supper		
Meat or substitute unsalted*	Unsalted cold beef	60	2 ounces
Potato or substitute unsalted*	Baked potato with unsalted butter	100	1 medium
Vegetable unsalted*	Unsalted buttered green beans	75	½ cup
Salad*	Celery and carrot sticks	60	3 to 4 of each
Fruit*	Sliced banana	100	1 medium
Beverage	Milk	240	½ pint
Bread, unsalted*	Unsalted bread	25	1 slice
Butter unsalted*	Unsalted butter	7	1 square
Cream	Cream 20%	50	3 tablespoons
Sugar	Sugar	15	1 tablespoon

* Note limitations listed in Table 123

eral, the consensus at present appears to be that the benefits to be derived in the management of essential hypertension by rigid restriction of salt are not sufficient to render worth while the general use of this form of treatment alone, but that considerable value may be derived by the combination of moderate restriction of salt with other forms of antihypertensive therapy

In summary, no dietary treatment is known that has any specific favorable effect on the course of essential hypertension The patient who has essential hypertension should eat as much as is necessary to maintain strength and nutrition but should avoid excesses This restriction of the quantity and quality of the diet should be extended to total calories, total volume of fluids, protein and salt *Moderation* as a watchword should apply to the diet as well as to all other aspects of treatment

CONGESTIVE CARDIAC FAILURE

The basic aims in the management of cardiac disease are (1) to reduce the work load of the organ as much as possible and (2) to put the organ at rest Ingestion of food increases cardiac work Moreover it is also probable that the heart functions at a disadvantage after a heavy meal because, with distention of the stomach, the diaphragm is elevated and the heart is displaced upward Obesity constitutes a handicap to circulation and respiration that, in the presence of cardiac failure may become a serious factor due to elevation of the diaphragm decrease in volume of the lungs and change in position of the heart Adiposity of the cardiac muscle may be another factor in the impairment of adequate myocardial function Furthermore, it has been shown that obesity increases the work of the heart during exertion, for the skeletal musculature must move a larger mass Therefore, one of the foremost aims of a dietary program for cardiac disease, particularly if the patient is suffering from cardiac failure, is reduction in body weight if the patient is obese It calls for a diet low in calories that will serve not only to eliminate excess weight but also to maintain cardiac work at as low a level as possible

Since it is known that undernutrition decreases bodily consumption of oxygen with resultant decrease in cardiac work, one would expect a diet low in calories to be especially useful in the treatment of congestive cardiac failure for such reasoning is in line with the previously stated basic aims in the management of cardiac disease Physicians were aware of the fact that calorically restricted diets were of value in the treatment of cardiac failure long before the theoretic basis for such diets was understood Karell,[16] in 1866, introduced the diet that bears his name and that consists solely of 800 cc of milk daily Such a program frequently has been found to result in great diuresis, remarkable improvement in myocardial efficiency and alleviation of symptoms Some workers have advocated institution of the Karell diet for three to seven days in the early stages of congestive cardiac failure, followed by a diet restricted to 800 to 1,200 calories per day, the duration for which such a diet is to be continued is determined by the progress of the patient and the amount of weight to be lost

Although no indication exists for drastic reduction of the intake of protein in the diet, the effect of the specific dynamic action of protein with the resultant extra demand for energy placed on the heart requires that the daily intake of protein for an adult patient of average size suffering from congestive cardiac failure should be moderate and should approximate an amount sufficient to keep the patient within safe boundaries of positive nitrogen balance, this amount is 60 to 70 gm. daily.

In congestive cardiac failure, the myocardium fails to perform adequately its function of propelling blood through the circulatory system. Consequently, a disproportionate amount of blood is usually present in that part of the vascular system concerned with the right side of the heart, venous return is retarded and stasis results. In turn, fluid is diffused from the blood stream through the walls of the blood vessels into tissue spaces of the lungs and liver and into the peripheral tissues—in fact, into all parts of the extracellular fluid compartment of the body. Impaired excretion of sodium by the kidneys results in retention of salt in these tissues, which further increases storage of excessive amounts of water in the tissues because of the water-binding properties of sodium.

Warren and Stead[16] were able to produce edema in patients who had recovered from previous episodes of congestive cardiac failure by adding an excessive amount of salt to their diets. Under these circumstances, typical symptoms and signs of congestive cardiac failure again developed. These investigators concluded that edema which develops in patients who have congestive cardiac failure is due to decreased cardiac output. The kidneys are unable to excrete salt and water adequately, and the excess of sodium and water is stored in tissue spaces as edema fluid. As a result of this series of events, the other symptoms and signs of cardiac decompensation develop.

Despite the fact that controversy still exists regarding the pathogenesis of congestive cardiac failure and regardless of whether one accepts the "forward" or the "backward" theory, the work of Warren and Stead served to focus attention on the importance of the sodium ion in the genesis of cardiac edema. For years, it has been known that patients suffering from cardiac disease have difficulty in excreting sodium in a normal manner, although the value for sodium in serum does not increase. However, renewed interest in the use of diets low in salt for patients suffering from congestive cardiac failure was brought about by the observations of Barker,[17] by the work of Warren and Stead, and by the studies of Schroeder,[18] Schemm,[19], Wheeler and associates [20] and others who have advocated an acid-ash diet sharply restricted in salt but with an abundant allowance of fluid. This form of treatment, in conjunction with the administration of digitalis in one of its various forms, the use of mercurial diuretics and the employment of other commonly accepted measures in the management of congestive cardiac failure, has proved to be extremely efficacious and has gained widespread acceptance.

Further studies have indicated that restriction of ingested salt to 1.5 to 2.0 gm. daily is the most important feature of the program. Clinical experience further has shown that diuresis may be enhanced by the free ingestion of fluid, depending on the desire of the patient, up to 2,500 to

3,000 cc daily It has been our practice to employ such a diet in the majority of cases, that is, to allow approximately 0 5 gm of sodium (1 3 gm of sodium chloride) daily with unrestricted fluid in the management of patients who have congestive cardiac failure with edema (Tables 120, 123 and 124) Occasionally, a patient with cardiac failure is encountered in whom edema, both pulmonary and peripheral appears to be refractory

TABLE 125 —FOODS INCLUDED AND EXCLUDED IN THE 2 0-GM SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE

Type of food	*Foods included*	*Foods excluded*
Beverage	Carbonated beverage cereal beverage coffee milk milk drinks tea	None
Bread	Any with emphasis on whole-grain or enriched bread except those excluded	Salted crackers, soda crackers, restricted use of quick breads and rolls
Cereal	Any with emphasis on whole-grain or enriched cereal	None
Dessert	Cakes, cookies custards gelatin desserts ice cream rennet desserts puddings sherbets	Rich pastries
Fat	Butter and substitutes cream salad dressing salad oil shortening fortified margarine	Bacon fat
Fruit	Any fruit or juice including one citrus fruit or other food high in vitamin C daily except those excluded	Raw apples cantaloupe, honey dew melon watermelon
Meat egg or cheese	Any meat fish or fowl except those excluded eggs cottage cheese cream cheese	Salted or smoked meats fish or fowl bacon cheeses other than those included
Potato or substitute	Potato hominy macaroni noodles, rice spaghetti	Fried potato potato chips
Soup	Cream soup	Bouillon broth soups made with broth
Sweets	Candy honey jam jelly sugar sirup molasses	None
Vegetable	Any except those excluded	Salted pickles sauerkraut, dried beans broccoli Brussels sprouts cabbage cauliflower cucumbers kohlrabi dried peas green peppers onions radishes rutabagas turnips
Miscellaneous	Chocolate, cocoa white sauce unsalted nuts spices and vinegar in moderation herbs peanut butter unsalted popcorn	Gravy salted nuts olives salted pickles, salted popcorn relishes salt except small amount in cooking

to treatment It is not unusual to encounter such a situation in patients who have far-advanced myocardial disease many such patients have had repeated episodes of congestive cardiac failure In these patients it may be found that diuresis will not proceed satisfactorily or clinical improvement ensue until the amount of sodium in the diet is reduced to 0 2 gm (0 5 gm of sodium chloride) daily (Tables 120 121 and 122) Contrariwise patients are occasionally encountered in whom cardiac failure is more

than usually amenable to treatment, in such instances, diuresis may be accomplished and clinical improvement obtained with a more liberal dietary program containing 2.0 gm. of sodium (5.0 gm. of sodium chloride) daily (Tables 120, 125, 126). For the most part, however, the diet providing 0.5 gm. of sodium (1.3 gm. of sodium chloride) and 70 gm. of protein daily is the one of choice.

TABLE 126.—DIETARY PATTERN AND SAMPLE MENU FOR 2.0-GM. SODIUM DIET IN THE DIETARY PROGRAM FOR CARDIOVASCULAR RENAL DISEASE*

Dietary pattern	*Sample menu*	*General Diet*	
		Wt. gm.	*Approx. measure*
	Breakfast		
Fruit	Grapefruit	100	½ medium
Cereal	Whole-grain cereal	15 (dry)	½ cup (cooked)
Egg	Soft-cooked egg	50	1
Bread	Whole-wheat toast	25	1 slice
Butter	Butter	7	1 square
Beverage	Coffee		1 cup
Cream	Cream (20%)	75	⅓ cup
Sugar	Sugar	15	1 tablespoon
Jelly	Jelly	20	1 rounded tablespoon
	Dinner		
Meat†	Roast beef	60	2 oz.
Potato†	Mashed potato with butter	100	½ cup
Vegetable†	Buttered beets	75	½ cup
Salad	Sliced tomato	75	½ medium
Salad dressing	Mayonnaise	15	1 tablespoon
Dessert	Vanilla ice cream	70	⅓ cup
Beverage	Milk	240	½ pint
Bread	Whole-wheat bread	25	1 slice
Butter	Butter	7	1 square
	Supper		
Meat or substitute†	Cold roast beef	60	2 oz.
Potato or substitute†	Baked potato with butter	100	1 medium
Vegetable†	Buttered green beans	75	½ cup
Salad	Celery and carrot sticks	60	3 to 4 of each
Dessert	Sliced banana	100	1 medium
Beverage	Milk	240	½ pint
Bread	Whole-wheat bread	25	1 slice
Butter	Butter	7	1 square

* No salt shaker is placed on tray or at table. These diets also may be ordered with varying protein content. The sample menus will be similar to those given for the sodium poor diets, except that food will be salted in cooking.

† Note limitations listed in Table 125.

Barker, Schemm and others have advocated, in addition to restriction of sodium, that the diet be of acid-ash composition in order to accomplish optimal diuresis. We have thought that the acid-ash diet is not particularly palatable; in some instances, this fact poses rather difficult dietetic prob-

lems Thus, we have relied on the use of "acid-salt" diuretics, such as ammonium chloride, potassium nitrate or potassium chloride, in doses of 2 to 3 gm three times daily, to augment other diuretics and produce the desired acidifying effect However, such diuretics should be used with great caution, if at all, unless the ability of the kidneys to excrete nitrogen is normal or near normal

Depletion of Salt—Any diet in which the amount of salt is drastically restricted presents the problem of possible harmful effects that may result from deficiency of sodium or chloride, especially if a defect is present in the resorptive function of the renal tubules, which may prevent adequate conservation of salt This is especially true in patients who have congestive cardiac failure, because of the loss of salt that accompanies diuresis in the course of treatment of these patients The clinician who employs such a regimen must be constantly on the alert especially in elderly patients, in evaluating complaints of weakness, lassitude, anorexia, nausea and vomiting mental confusion abdominal cramps and aching in skeletal muscles as possible indications of impending disaster in the form of depletion of salt Patients consuming such diets must be kept under frequent and close observation especially in warm weather when excessive amounts of salt may be lost through perspiration

In summary, the diet in the treatment of congestive cardiac failure should be adjusted to maintain the dry body weight at normal or slightly below normal levels it should be well balanced light and nutritious with adequate easily assimilated carbohydrates a moderate amount of protein, sufficient fat to meet caloric needs an adequate content of vitamins and restriction of salt as indicated In the selection of food, consideration should be given to the patient's likes and dislikes Fried or greasy foods should be avoided, as should spices and condiments and foods tending to produce flatulence Meals should be eaten slowly and thoroughly masticated In many cases, 5 or 6 small meals daily are to be preferred to 3 large ones Constant vigilance should be maintained against symptoms of depletion of salt in all patients who are to be maintained for a prolonged period on a diet restricted in salt [1]

ACUTE MYOCARDIAL INFARCTION

Early in the course of acute myocardial infarction, the type of diet indicated must be governed by the extent of myocardial damage and the condition of the patient *Absolute rest in bed* is of prime importance the patient s output of energy should not be taxed in any way during the early stages, and he should be maintained at conditions that are as near basal as possible He should not be allowed to feed himself or to roll over in bed unassisted The bowels should be kept as regular as possible by means of mild laxatives or enemas if necessary straining at stool should be avoided Whether a bedpan or a bedside commode occasions the lesser degree of exertion is a moot question and its solution must be left to the judgment of the clinician

In the first two or three days the diet must be light In most cases, a liquid diet with a volume of 1,000 to 1,500 cc per day is indicated but in

some patients, critically ill, no food should be urged Such a patient may wish only small amounts of fluid at a time—water, ginger ale, milk or tea Care should be taken to avoid abdominal distention in patients who do not tolerate milk well When milk is tolerated, the Karell diet (200 cc of milk 4 times daily) may be employed for two or three days Should evidence of congestive cardiac failure be present, the intake of sodium should be restricted In the event of persistent and distressing vomiting in the early days after acute myocardial infarction, small amounts (50 to 100 cc) of hypertonic solution of dextrose (10 to 20 per cent) may be given intravenously with caution at regular intervals during the day to provide adequate fluid and carbohydrate It may be necessary to give isotonic solutions of sodium chloride or dextrose subcutaneously with as little disturbance to the patient as possible Large intravenous infusions of any sort are contraindicated because of the extra load they impose on a damaged myocardium and the hazard of pulmonary edema

As soon as it can be tolerated, the intake of fluid may be supplemented with a diet consisting of soft foods, such as cooked cereal, soft-boiled or poached egg, milk toast, simple puddings, soup, baked potato and stewed fruit Feedings, however, should be in small amounts, given at fairly frequent intervals if necessary

After the acute phase has passed (or in mild cases from the onset), it is reasonable to allow a diet of 800 to 1,200 calories, which may be gradually increased as the patient is finally allowed to get out of bed and resume some degree of activity When the patient finally resumes moderate activity, the caloric content of the diet should be adjusted so as to maintain weight at normal or near normal levels, or should be kept restricted in calories in order for the patient to reduce if he is overweight Under ordinary circumstances the patient may eat 3 meals daily, however, in some patients who experience dyspnea or anginal pain at rest or with effort after a meal, it may be desirable to divide the daily caloric intake into 5 or 6 smaller feedings

At all times, these diets should be kept adequate in vitamins by the addition of supplemental vitamins in the form of a multivitamin capsule daily Care should be taken, as in patients who have congestive cardiac failure, that foods which have a tendency to cause abdominal distention are avoided As has been mentioned previously, the intake of salt in the diet should be sharply curtailed if the presence of congestive cardiac failure complicates the situation

ARTERIOSCLEROTIC HEART DISEASE

In the brief span of time between publication of the first edition of this book and the present edition, thinking among investigators in the field has been clarified and brought more sharply into focus Accumulated data seem to suggest a substantial relationship between obesity and caloric intake cholesterol and the unsaturated versus saturated fatty acids content of the diet of the patient who has arteriosclerotic cardiac disease For a more complete discussion the reader is referred to the section on 'The Role of Nutrition in Atherogenesis"

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Chapter 26 (*Continued*)

B Nutrition in Relation to Atherosclerosis

By Gerald J Friedman

Introduction —In any discussion of nutrition and atherosclerosis it is essential to define clearly the factors being studied Some studies report the relationship between diet and serum lipids, others between diet and atherosclerosis, still others between serum lipids and atherosclerosis The literature contains studies which relate nutritional factors to the *incidence* of ischemic heart disease others relate it to the *mortality* from coronary thrombosis, while still others relate it to deaths *from all atherosclerotic* diseases In order to obtain valid correlations, similar factors must be studied

Definition —It is essential that the terminology be clearly defined since much confusion has resulted from the inclusion of different lesions under one term Arteriosclerosis is the all inclusive term denoting a number of different processes which produce thickening of the arterial wall [1] Klotz in defining arteriosclerosis, suggested that *all* scleroses or hardening of the arteries be included under the general term, with other varieties or entities being recognized [2] Boyd stressed the need for dividing the subject into 3 sections atherosclerosis, Monckeberg s sclerosis and diffuse arteriolar sclerosis [3] Sappington and Cook studied varieties of arteriosclerosis and found that diffuse intimal thickening, and Monckeberg s medial sclerosis were unrelated to the presence or absence of atherosclerosis [4]

Hyperplastic arteriosclerosis (diffuse arteriolar sclerosis, or diffuse intimal thickening) is associated with hypertension and affects the small arteries and arterioles The result is a thickened vessel wall with a uniformly narrowed lumen It is unrelated to the presence or absence of atherosclerosis

Monckeberg's sclerosis is due to medial calcinosis and leaves the lumen of the vessels unobstructed thus resulting in the absence of symptoms and a good prognosis

Marchand coined the term atherosclerosis to designate the soft amorphous lipid accumulation in the intima [5] The lesions are usually scattered in distribution and are localized They consist of intimal plaques which are formed by connective tissue proliferation and the deposition of lipids *The lesions tend to enlarge, encroaching upon the lumen, causing the formation of thrombi* Progression of the atherosclerotic process results in narrowing of the vessel with resultant intravascular thrombosis, a rupture of the plaque or hemorrhage into it, any of which may occlude the vessel

Pathology of Atherosclerosis —Yater lists the following pathological findings in early atherosclerosis [6]

(1) Simple plaque formation the plaque being composed of moderately loosely arranged connective tissue, frequently containing young fibroblasts
(2) The presence, only occasionally, of a small nidus of amorphous material in the plaque
(3) Few, if any, cholesterol crystals in the plaque
(4) Slight to moderate damage to the internal elastic lamina which usually may be identified
(5) Slight thinning with minimal interstitial fibrosis of the media below the plaque

Moderately advanced atherosclerosis has the following characteristics
(1) Hyalinized base of the plaque
(2) Presence of a large mass of the amorphous cholesterol or lipids in the plaque
(3) Surface of the plaque composed of compact fibrous tissue in which a few fibroblasts persist
(4) Minimum calcium deposition in the center of the plaque usually in the form of fine calcium granules
(5) Presence of a few cholesterol clefts
(6) Slight marginal vascularization
(7) Fragmentation or frequent absence of internal elastic lamina
(8) Moderately thin, occasionally vascularized, media with loss of muscle fibers and increased fibrosis below the plaque

Advanced atherosclerosis results in
(1) Complete, or almost complete, hyalinization of the plaque, both base and surface zones with fibroblasts remaining only at the margin
(2) Masses of calcium in the plaques
(3) Frequent presence of cholesterol clefts
(4) Common presence of broad vascular channels at the margin and base of the plaque
(5) Absence of or severe damage to, the internal elastic lamina, and
(6) Hyalinization or atrophy of media with loss of muscle and increase in fibrous tissue

The Chemistry of Atherosclerosis —The recent review by Schroepfer is highly recommended [10]

The high lipid content of atheromatous plaques supports the hypothesis that lipids play a role in the pathogenesis of atherosclerosis Veek and Buck and Rossiter have shown that pathologic sites contain large amounts of lipid material and cholesterol [8] They have demonstrated that with increasing severity of the atheromatous process not only the total extractable lipid and cholesterol content of the aortic tissue but also the total fatty acid content of the involved areas increase Although the total quantity of fatty acid increases the proportion of fatty acids to the total lipid content of the tissue decreases with increasing severity [9] The ratio of free to esterified cholesterol rises with increased severity As the atheromatous process increases in severity, the lecithin and sphingomyelin fractions of the phospholipids increase whereas the cephalin and the galactolipid fractions of the phospholipids decrease in proportion to the total

extractable lipid of the involved tissue. McArthur[11] studied the fatty acid composition of atheromatous lesions. The saponified product of the acetone-soluble (phospholipid-free) atheromatous aortic tissue, had the following composition: stearic 2.9 per cent, palmitic 14.6 per cent, oleic (as well as other highly unsaturated acids that escaped precipitation when brominated) 65.2 per cent, linoleic 9.4 per cent, arachidonic 2.1 per cent and petroleum insoluble acids 5.8 per cent. Tuna[1] found a higher percentage of linoleic acid than other lipid fractions in the cholesterol esters of atherosclerotic plaques. The epiphasic carotenoids, which contribute to the yellow color of the atheromata, increase with the age and extent of the lesions.[13]

The entire aorta (not only the atheromatous lesions) shows an increase in lipid content with age. This change is lipid composition with age is confined to the media. In atherosclerosis the increased lipid content is found in the intima.[8,9] No relationship has been found between the cholesterol content of the serum and the total extractable lipid in the aortas of patients with normal lipid values.[14,15] However in cases of atheromatosis associated with hypercholesterolemia Faber did report a marked increase in the cholesterol content of the aortas.[16]

EXPERIMENTAL ATHEROSCLEROSIS

An excellent review of experimental atherosclerosis has been written by Katz and Stamler, and is required reading for this subject.[3]

Anitschkow, in 1913, produced atherosclerosis by feeding cholesterol to the rabbit. Since then, experimental atherosclerosis also has been produced and studied in the chicken,[17] guinea pig,[18] dog,[19] and monkey.[20,21] Katz and his co-workers selected the chick as an experimental animal in order to obviate some of the criticisms levelled at the use of the rabbit in studying atherosclerosis. The chick is omniverous and develops atherosclerotic lesions of the great vessels spontaneously. Early studies showed that cholesterol feeding led to hypercholesterolemia and eventually atherogenesis. The atherosclerosis involved not only the aorta but also the major systemic vessels including the coronaries. Cholesterol was readily shown to be the decisive atherogenic stimulus in chicks as in rabbits.

The similarities and differences between experimental atherosclerosis in animals and human atherosclerosis have been recorded.[2] The localization of the lesions is different in rabbits as compared with man. The most severe lesions appear in the thoracic aorta of the rabbit, as compared with the abdominal aorta in man. The aorta and pulmonary artery are prominently involved in the rabbit, the cerebral and retinal vessels being spared. In man the cerebral and retinal vessels are involved while the pulmonary artery is spared. Another difference is the enlargement of the liver and spleen which occurs in cholesterol induced atherosclerosis in the rabbit due to the accumulation of cholesterol in the reticulo-endothelial cells, but not in humans.

The amount of cholesterol that must be fed to animals to produce lesions is much higher than the intake of man even on a high cholesterol diet. To be equivalent to the diet fed rabbits (5 mg. cholesterol per calorie) a

human diet of 3000 calories would require 15 grams of cholesterol or 10 to 20 times more than man consumes even on a high cholesterol diet In the chick, prolonged cholesterol feeding induces the same type of atherosclerotic changes which are found in the human lesions, including foam cell plaques necrosis atheromatous abscesses, fibrosis hyalinization, calcification and cartilaginous osseous metaplasia The only lesion not produced in the cholesterol fed chicks is ulceration of the atherosclerotic plaque with thrombus formation Duff and McMillan noted the remarkable similarity in the gross and microscopic pictures of the lesions in experimental animals and humans[27] Katz states, "even the most severe critics of the cholesterol concept of atherosclerosis cannot fail to note the conspicuous similarities between cholesterol induced lesions, whether in rabbit common dog, or chick and the lesions seen in man Taking into consideration the anatomic differences among the various species in architecture of the great vessels, the similarities between experimental cholesterol induced and human lesions are indeed remarkable "[28]

Experimentally induced atheromata can be prevented from developing or may be made to regress, by cessation of cholesterol feeding[4 25] In dogs, atheromata produced by the feeding of cholesterol and thiouracil regress when these two substances are removed from the diet[6] Reduction of the total caloric content of the diet in the face of an absolute cholesterol content similar to controls did not reduce the induced type of cholesterolemia and atherosclerosis in rabbits, but even appeared to aggravate the process[7] Katz and his colleagues showed that cholesterol fed birds starved during alternate periods developed marked hypercholesterolemia and atherosclerosis resembling the findings in chickens on a continuous cholesterol-mash diet In contrast the chickens alternating between the cholesterol diet and regular mash exhibited only slight hypercholesterolemia and atherosclerosis Thus, intermittent periods of starvation hindered the disposal of the exogenous cholesterol load whereas intermittent periods of regular mash facilitated such disposal These findings suggest the possibility that in man the effects of exogenous cholesterol on cholesterolemia and atherogenesis may be regulated at least in part, by overall nutritional status

Kritchevsky and his colleagues[8] showed that the severity of atheromata in cholesterol fed rabbits was decreased if poly-unsaturated fatty acids were used in place of stearic or oleic acid as the base for the cholesterol in the diet although the hypercholesterolemia produced by the cholesterol feeding was not reduced

Hormonal factors influence experimental atherosclerosis Thyroid reduced the hyperlipemia of cholesterol fed and stilbestrol administered chicks, and effectively inhibited the development and severity of cholesterol induced atherosclerosis in the chick[29 30] The mechanism of the effect is unknown but may be due to hepatic degradation of the lipids resulting in lipid depletion It is unrelated to the hypermetabolic state, since dinitrophenol had no effect on hyperlipemia or atherogenesis

Estrogens were remarkably effective in prophylactically inhibiting the development of coronary atherosclerosis They caused a rise in phospholipemia without influencing cholesterolemia, resulting in a fall in plasma

C/P ratios toward normal Although the coronary atherosclerosis was inhibited by estrogens, lesions in the aorta were unaffected [31 32] Pick *et al* also demonstrated that estrogens were effective therapeutically in reversing coronary atherosclerosis induced in cockerels by cholesterol feeding [33]

The relationship of the pancreas to atherogenesis has been studied in the dog, rat, rabbit and cockerel, by pancreatectomy and alloxan-induced diabetes Duff and McMillan[34] and Pierce[35] showed that alloxan diabetic, cholesterol-fed rabbits have a hyperlipemia and hypercholesterolemia but show less atherosclerosis than normal cholesterol-fed animals This is felt to be due to alterations in the plasma lipoprotein pattern

Stamler and his co-workers in Katz' laboratory demonstrated the need for the addition of neutral fat, in the form of cottonseed oil supplements, in order to produce hypercholesterolemia in pancreatectomized, cholesterol-fed chicks [36]

The effects of pituitary and adrenal hormones in experimental atherosclerosis have also been reported Stamler *et al* found that cortisone potentiates atherogenesis in the chick when accompanied by an atherogenic level of cholesterol intake [37] In the rabbit, cortisone has been shown to inhibit cholesterol atheromatosis [38] Desoxycorticosterone acetate alone was found to have no effect on cholesterol induced atherosclerosis in rabbits,[39] and chicks [40] The luteinizing hormone and follicle stimulating hormones were without influence in cockerels [41]

Cholesterol atherosclerosis in the rabbit has also been inhibited by the administration of adenosine triphosphate[42] and potassium thiocyanate [43] Cholesterol elevation and atherosclerosis has been prevented in the cholesterol-fed chick by the addition of dihydrocholesterol to the diet [44] It is believed to act by interfering with cholesterol absorption Ferric chloride also inhibits the severity of atherosclerosis in cholesterol-fed chicks Its action is thought to be through the formation of an insoluble precipitate with bile salts which are known to be essential for the absorption of cholesterol [45]

Stamler *et al* showed that the lipotropic factors choline and inositol failed to reduce the incidence or severity of cholesterol induced lesions in the aorta of the chick [46] Firstbrook[47] and others similarly found choline to be ineffective as a prophylactic or therapeutic agent against cholesterol induced atherosclerosis in rabbits and dogs

Restricting the intake of fat reduces the development of aortic athero sclerosis in cholesterol fed chicks [48] Horlick *et al* showed that exogenous lipid was not essential for the development of spontaneous atherosclerosis of the chicken but that it accelerated the process [49] Stamler and Katz noted that hypertension, induced by salt, or desoxycorticosterone and salt, was not an atherogenic stimulus *per se* This finding was in accord with observations with other species including the rabbit, dog, sheep and goat However the desoxycorticosterone-salt hypertension did intensify the cholesterol-induced atherogenesis in cholesterol-fed cockerels This, too, was found in rabbits and dogs

Vascular damage is not necessary in the experimental animal for the production of atherosclerosis nor does it, by itself, result in atherosclerosis [50]

However injury to the vessel wall does result in an intensification of the atherosclerotic process at the sites of injury [51 5]

There are many species differences in the development of atherosclerosis Man, the chicken and duck develop atherosclerosis spontaneously The dog and rabbit rarely do Experimentally gross atherosclerosis is easy to produce in rabbits and chicks It is more difficult in guinea pigs, hamsters and ducks as well as cats and rats In general, ease of hypercholesterolemia production and ease of atherosclerosis production parallel each other among the various species

PATHOGENESIS OF ATHEROSCLEROSIS

The exact mechanism by which lipid is deposited in the vessel wall is still unknown Many theories have been postulated

Virchow originally postulated that lipids were deposited in the intima by direct infiltration from the plasma Weinhouse and Hirsch showed that the proportions of the various lipid fractions in the atheromatous lesion resemble those of the serum [53]

Comparison of Lipid Composition of Blood Plasma and Arterial Tissue

	Percentage of Total Lipid		
Lipid	*Blood Plasma*	*Intima*	*Early Plaque*
Free cholesterol	14 1	14 2	16 2
Cholesterol esters	38 3	38 6	38 5
Phospholipids	22 8	20 1	19 0
Neutral fat etc	23 3	27 1	26 3

These figures suggest that the lipids deposited in the intima are the result of nonselective infiltration and precipitation of the various lipids from the plasma

Other investigators believe that phagocytosis of larger lipid aggregates by the intima is a prime initial step in atherogenesis Heuper[54] produced atheroma like lesions in dogs by the injection of macro molecular suspensions of colloids such as polyvinyl alcohol, methylcellulose, acacia and pectin The endothelium phagocytized the foreign body and proliferated locally as foam cells which contained the injected colloid and not cholesterol Further penetration of these cells led to degeneration of the media with hyalinization and disintegration of the elastic fibers Heuper postulated the anoxemia theory of atherosclerosis He felt that cholesterol circulates in the blood stream, possibly in the form of macromolecules Due to an imbalance of the plasma colloid equilibrium cholesterol is deposited as a film on the intima This film interferes with the nutrition of the endothelium resulting in increased permeability of the endothelial lining and proliferation of the endothelial cells which take up cholesterol and are converted into foam cells A similar conversion into foam cells takes place in the subendothelial space where the cholesterol in the plasmatic fluid is phagocytosed by histiocytes

Hirsch and Weinhouse similarly believe that an increase in particle size of plasma lipoprotein aggregates leads to phagocytosis by intimal cells.[55] They suggest that the cause of the precipitation of lipid in humans is mainly a tissue factor enhanced by hyperlipemia.

Many authors have stressed the importance of vessel wall damage in the pathogenesis of atherosclerosis. Faber[56] found that with increasing age the aorta develops an increasing amount of metachromatically stainable carbohydrate-sulfuric-acid esters, which he believes play a role in the deposition of cholesterol and the formation of atherosclerotic plaques. Dock and Duff also stress the importance of vascular wall damage in atherosclerosis, although Duff postulates the possibility of the hypercholesterolemia being the causative factor in the vascular wall injury.[57,58] Hueper's theory also implicates vascular damage as an important factor in atherosclerosis. Here the vascular damage is secondary to the anoxemia caused by the deposition of the cholesterol film. Pollak[59] noted intimal changes after shock, with resultant seepage of plasma through the damaged endothelium. After the breakdown of lipoproteins and resorption of most of the foreign material, cholesterol remains in the subintima, where it acts as an irritant and initiates atherosclerosis.

Hueper, Hirsch and Weinhouse, and Pollak postulated that intimal cells have lipid phagocytic capacities. Leary, however, hypothesized that the cholesterol containing chylomicra are phagocytosed by reticulo endothelial cells, which become detached and are attracted to the intima by chemotaxis. They then penetrate the endothelium due to the force of the blood stream and form foam cell cushions—or atheromata, the initial lesion of atherosclerosis.[60] The foam cell then breaks down, releasing the lipid which is phagocytosed by the fibroblasts of the arterial wall. The ability to dispose of this lipid decreases with age and, as a result, cholesterol esters accumulate, resulting in the reactive and degenerative processes ending in the fully developed plaque. Simonton and Gofman[61] blocked the reticulo-endothelial cells in rabbits with radioactive thorium and found no radioactivity in the atherosclerotic plaques of the aorta resulting from cholesterol feeding. Since there was a high radioactivity in the Kupfer cells and in the macrophages of the spleen and bone marrow, it appears that the foam cells in the atherosclerotic plaques are not derived from the phagocytic cells of the reticulo endothelial system. Studies by Duff and MacMillan[6] also fail to support Leary's theory of the origin of lipophages.

Winternitz *et al* attributed the primary change in atherosclerosis to hemorrhage from the vasa vasorum.[63]

Duguid recently focused new attention on the "Thrombosis" theory of Rokitansky that atherosclerosis is initiated by deposits of fibrin on the inner walls of the arteries, after which a layer of intimal cells covers the fibrin layer, incorporating it into the vessel wall. The incorporated fibrin also contains thrombocytes, erythrocytes and leukocytes. Secondary intimal proliferation and fatty changes then occur in these deposits.[64]

The theories of Winternitz and Duguid have not been confirmed by the experimental studies of Wartman. He injected homologous blood into the arterial media of dogs and was unable to produce atheromatous changes in the intima.[6]

Groen and Van der Heide suggest that a combination of several theories may provide a closer approximation to the problem[66] "The emphasis on macromolecules is in accord with the modern cholesterol theories since cholesterol circulates in the plasma in the form of protein lipid complexes As the macromolecules are forced into the wall of the arteries by the arterial pressure, especially at sites of increased centrifugal force of the blood stream, localization of the lesion may be determined It is likely that lipoproteins are deposited more easily in a vessel wall damaged with intimal proliferation exudates and hemorrhage and once deposited, are more difficult to remove The deposits of protein can be dissolved while the cholesterol must be phagocytized before being removed When the amount of locally deposited cholesterol is too large or when the vascular damage is severe the macrophages deteriorate locally liberating cholesterol into the tissue From this stage on a number of processes probably parallel and overlap producing exudation and hemorrhage The process leads to hyalinization organization intimal proliferation new formation of capillaries, necrosis repeated hemorrhage ulceration calcification and finally to thrombosis Add to this the characteristic elastica changes ("elastosis") seen at older ages, and the well known protean and accepted picture of atherosclerosis is defined "

Experimental evidence has been obtained supporting the theories that these processes are involved in the development of atherosclerosis Wilens[67] distended human arteries under various pressures with normal human blood serum and was able to confirm the deposition and retention of cholesterol within the arterial wall Evans pulsated blood at various pressures against strips of human aorta Blood from normal individuals resulted in little or no lipid deposition while that from atherosclerotic individuals resulted in more marked lipid deposition[68] Hass and Taylor[69] demonstrated experimentally the importance of vascular damage in the localization of atherosclerosis They damaged the aorta of rabbits by freezing, with resultant necrosis and regeneration by local hyalinization and calcification The changes resembled human arteriosclerosis since there were no fat deposits or intimal proliferation However, when the same experiment was performed in rabbits on a high cholesterol diet atheromatosis developed in the damaged vessel wall

Rutstein and his co workers recently demonstrated the intracellular deposition of lipid in tissue cultures of human aortic cells when cholesterol was added to the culture medium[70] They showed that *in vitro*, linoleic acid (a polyunsaturated fatty acid) prevented the deposition of lipid induced by cholesterol They concluded that in the tissue cultures in a medium containing human blood serum deposition of lipid can be (1) Induced by adding cholesterol (2) Reversed by replacing the cholesterol-containing medium by normal medium (3) Prevented by adding linolenic acid (4) Potentiated by adding stearic acid (a saturated fatty acid)

SERUM LIPID LEVELS

Cholesterol* —The normal level of plasma cholesterol in adults or children living on a diet of vegetables and fish is between 120 to 160 mg

*Cholesterol metabolism see Chapter 8

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per cent Clinical experience has shown that atherosclerosis and coronary heart disease are minimal and intravascular thrombosis is rare when the diet is such as to maintain blood cholesterol levels below 180 mg per cent[71] In those countries where the blood cholesterol is over 220 mg per cent in the middle aged males, a problem of coronary heart disease exists (death rates above 350 per 100,000)[72] Gofman reported a co-operative study involving 4000 men aged 40 to 59 years Within one to two years, those whose serum cholesterol levels were in the upper third had three times the number of new events as those whose levels were in the lower third[73] In the Framingham study, Dauber *et al* showed the increased risk of ischemic heart disease associated with high serum cholesterol[74] Males with serum cholesterol levels above 260 mg per cent had six times the incidence of new events compared with those whose levels were less than 225 mg per cent (80 per 1000 *vs* 13 per 1000) This risk was present even in the absence of two other important factors, namely hypertension and obesity

Cholesterol in free and esterified forms is higher in atheromatous arteries than in normal ones However, the cholesterol, phospholipid and neutral fat ratios in arterial walls are the same as those of blood plasma[75] leading some investigators to suggest the implication of other lipid abnormalities as pathogenic factors in atheromatosis[76]

Cholesterol-Phospholipid Ratio —Atheromatosis might not be due to the hypercholesterolemia *per se* but to a disturbance in the stabilization of the colloid state of cholesterol in the blood by factors favoring the precipitation of the cholesterol in plasma and tissues The insoluble hydrophobic cholesterol is carried in suspension in high concentration in the serum because of the presence of the hydrophilic substance, phospholipid, which keeps the cholesterol stabilized in the colloidal form Increases in the cholesterol beyond the equimolar state alter the colloidal stability of the lipid emulsion Peters and Man were the first to focus attention on the importance of the cholesterol phospholipid relationship[77]

Ahrens and Kunkel[78] emphasized that an increase of the cholesterol-phospholipid ratio was attended by increased atherosclerosis, while a low cholesterol-phospholipid ratio, even with a high cholesterol level, correlated with a low degree of atherosclerosis They correlated free cholesterol neutral fat, phospholipids and clarity of serum with skin lesions (xanthelasma and diffuse xanthomatosis) and atherosclerosis, based on clinical, electrocardiographic, roentgenologic and post mortem examinations Those patients without atherosclerosis, even in the presence of extensive xanthomatosis, had C/P ratios within, or lower than, normal Those with more atherosclerosis than expected for their age (on autopsy) had a C/P ratio higher than normal

Experimentally, Kellner *et al* and Payne and Duff showed the importance of the C/P ratio in the development of atherosclerosis in the rabbit[79, 80] The intravenous injection of Tween 80 and Triton A20 causes hyperlipemia in rabbits kept on a normal diet Both the cholesterol and phospholipid levels rise Rabbits given a high cholesterol diet and injections of the detergents intravenously developed higher levels of cholesterol but less atherosclerosis than the control group which received the same diet but no Tween The control group had no increase in the phospholipid concentration with a resultant increase in the C/P ratio

Duff[81] and his co-workers studying the effects of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit, came to the same conclusion regarding the inhibitory effect of phospholipid on cholesterol induced atherosclerosis Morrison and his colleagues,[8] Gertler *et al* [83] Pomeranze and Kunkel[84] and others have reported on the tendency for the cholesterol phospholipid ratio to be higher in coronary disease patients than in normals

Jackson and Wilkinson[8] doubt the usefulness of this ratio as an index of atherosclerosis Oncley [86] found that 30 per cent of the plasma cholesterol is in the alpha and 70 per cent in the beta lipoprotein fraction The *C/P* ratio of the alpha lipo-protein fraction is about 0 50 while that of the beta lipoprotein fraction is 1 34 In older men, especially those with athero-sclerosis diabetes, and xanthomatosis, the cholesterol increase is particularly in the beta lipoprotein fraction This increase is not always evident in the C/P ratio in the total serum

Gertler[83] felt that the cholesterol uric acid phospholipid ratio was of greater significance than the cholesterol-phospholipid ration The ratio is obtained by multiplying the level of the serum cholesterol by the level of the uric acid and dividing by the phospholipid level in the serum At the present time there is no explanation as to how cholesterol and uric acid interrelate in coronary artery disease

Alpha and Beta Lipoproteins —Barr and his colleagues studied the lipoproteins by means of Cohn's microfractionation method #10 By this *means alpha and beta lipoproteins are separated Patients with evidence* of atherosclerosis or coronary artery disease show a tendency to the reduction of the alpha lipoprotein fraction and an increase in the beta lipoprotein fraction These changes may be seen without hypercholesterolemia or elevation of the phospholipid ratio of the total plasma Barr feels that the cholesterol percentage of the beta lipoproteins is a better indicator of atherosclerosis than either the total cholesterol value, the C/P ratio of the total serum or the S f 10 to 20 flotation [87] Paper electrophoresis has been used in recent years for the determination of the lipoprotein pattern [88 89 91]

Lewis and Page[90] established a method of determining the alpha and beta lipoprotein by means of the ultra centrifuge The concentration of beta lipoproteins was found to increase with age males having a higher percentage of beta lipoproteins than females Patients with atherosclerotic complications also have a slightly higher beta lipoprotein value or a lower alpha lipoprotein value than normal controls The impression gained from these investigations is that the atherosclerotic influence of a high plasma level of cholesterol is related to the fraction of cholesterol circulating as beta lipoprotein

Macrochylomicrons —Moreton stresses the importance of post-prandial neutral fat hyperlipemia in atherogenesis [9] Macrochylomicronemia and gross lipemia occur following meals There is a marked increase in neutral fat with no change in cholesterol or phospholipid concentration Moreton believes that it is these large, coarsely suspended, colloidal particles containing cholesterol that are resistant to the normal removal mechanism of the arterial intima and which institute the formation of the foam cells [93]

Becker *et al* demonstrated that alimentary chylomicronemia is of significantly greater duration and intensity in people over 50 [94] Zinn and Griffith found a higher ratio of macro chylomicrons in the fasting blood sera of atherosclerotic patients as compared with normal controls [95] Block *et al* observed that following a standard fat meal men develop a significantly greater plasma lactescence than women of the same age group [96]

According to Moreton's concept, a qualitative alteration involving an increase in size of the cholesterol containing particles occurs Contrary to his theory, patients with normocholesterolemic, neutral fat hyperlipemia (*i e* idiopathic familial hyperlipemia or Von Gierke's glycogen storage disease) exhibit no unusual susceptibility to atherosclerosis, in contrast to those with *hypercholesterolemic hyperlipemia* [97]

High and Low Density Lipoproteins —Gofman and his associates have studied the giant molecules in the serum When large molecules in a colloid solution are subjected to ultra centrifugation, they will float or sediment depending upon their specific gravity in relation to the solvent Since lipoproteins possess a low specific gravity, Gofman added sodium chloride to raise the specific gravity of the serum further so that lipoproteins would float easily when subjected to ultra centrifugation [98] The velocity of the upward movement of the various fractions and their concentrations can be determined from the moving boundaries which can be made visible and be photographed during centrifugation As a unit of flotation velocity, Gofman uses the Sf unit (S equals Svedberg, f equals flotation) For example, when a macro-molecule floats upward with a velocity of 5 times 10^{-13} centimeters *per second per unit of field force*, the Sf value is 5, the *macro molecule* belongs to the Sf 5 class The Sf value gives information on the specific gravity of the macro-molecule but not its size The Sf 3 to 8 group occurs in any serum although the concentration of this fraction varies with the *individual* *The concentration of macro molecules* with a Sf value of 75 and higher increases after a meal rich in fat Chylomicra which consist predominantly of fat, have very high Sf

Gofman reported a good correlation of high Sf 10 to 20 levels in rabbits with experimental atherosclerosis, and in humans with atherosclerosis, myocardial infarction and diabetes mellitus He also showed that sera with blood cholesterol levels below 200 milligram per cent may show high concentration of molecules of the Sf 10 to 20 class while sera with cholesterol levels well over 200 milligram per cent may not show any measurable *concentration of Sf 10 to 20* class of molecules He used this variation in physical chemical properties of the lipoprotein molecules to explain the occurence of atherosclerosis in patients with both normal and elevated levels of cholesterol in the blood

Gofman later changed his Sf groupings and indicated the Sf 12 to 100 correlated with atherosclerosis, and still later, mentioned the Sf 12 to 400 as useful in differentiating normal from those with atherosclerotic tendencies

A cooperative study of lipoproteins and atherosclerosis done by a committee of the National Advisory Heart Council found no advantage in the use of Sf 12 to 20 or Sf 20 to 100 lipoprotein measures, or the related

atherogenic index,* over the simpler measurement of cholesterol, in the characterization of men prone to develop coronary heart disease[73] It was clear, however, that the mean values for both measurements were higher in the newly afflicted group than they were in the patients who remained well during the study Keys and others also report that the concentration of beta lipoproteins correlate no better with atherosclerosis than the total cholesterol level[99 100]

At the present time the most practical test to determine an abnormal tendency to develop atherosclerosis, if any test we have provides us with such information appears to be the serum cholesterol determination

DIET AND SERUM LIPIDS

There are multiple nutritional factors involved in the production of the lipid levels—(*i e* total calories, protein, fat carbohydrate minerals and vitamins)[101 10]

(1) Total Calories

(A) *Calorie Deficit*

Keys *et al*[103] showed that there were small but significant decreases in total cholesterol levels in young volunteers on a low calorie diet Kartin *et al*[104] reported a significant increase in cholesterol larger rises in phospholipids and critical changes in triglycerides in man during total starvation These changes were reversed by the ingestion of carbohydrate Rubin and Aladjem[105] demonstrated the following results of a four to five day fast in six healthy volunteers (1) no lipemia (the Sf greater than 400 lipoproteins did not appear) (2) marked increase in the Sf 12 to 20 and Sf 20 to 100 groups, (3) less marked increases in Sf 0 to 12 and Sf 100 to 400 groups and (4) no significant change in the high density lipoproteins These changes were reversed 24 hours after resumption of normal meals

Ahrens feels that "the incorporation of different dietary fats in subcaloric diets may have relatively little specific effect since the combustion of the semi starved patient's own adipose tissue comprises a large part of his total energy expenditure'

(B) *Calorie Excess*

The effect of excess calories on serum lipid levels has not been well defined Walker *et al*[106] demonstrated in two men that excess calories over a short period caused striking increases in serum cholesterol and lipoprotein levels even though the diet was low in fat Mann *et al*[107] showed that these increases could be prevented if sufficient exercise were taken to dissipate the excess food calories Anderson *et al*[108] found that a daily excess of 600 calories caused a significant elevation in the total serum cholesterol of 20 mgs per cent The hypercholesterolemia reached its peak

*Gofman adopted a formula for expressing an individual s atherogenic potentialities which he referred to as the index of coronary atherogenicity The formula is

$$A\ I = \frac{\text{Milligrams \% Standard Sf 0–12 plus 1 75x mgs \% Standard Sf 12–100}}{10}$$

The average atherogenic index varied with age and sex

at five weeks and was maintained unchanged for 15 more weeks despite a continuing gain in weight

Keys[109] showed that obese individuals do not have significantly higher blood cholesterol levels than normal weight individuals in those countries where the blood cholesterol level is low Gofman[110] also was unable to find differences in the sera of overweight versus underweight individuals

(2) Dietary Fat and Serum Lipids

(A) *Dietary Cholesterol*

Keys *et al* in 1956 came to the conclusion that dietary cholesterol has no important effect on serum cholesterol levels[111] This conclusion was based on (1) long term observations of men eating diets low and high in cholesterol (2) epidemiologic survey data in Minnesota and Sardinia where dietary intakes of cholesterol vary widely (3) experiments in which men doubled or halved their cholesterol intakes for many months (4) experiments in which 500 or 600 mg per day of cholesterol was added to a rice-fruit diet, and (5) experiments which tested three-fold variations in cholesterol intake in mixed food diets containing 66 grams of total fat per day They concluded that the independence of serum cholesterol levels and cholesterol intake demonstrated by them in adult men over the whole range of natural human diet probably also applied to infants, children and women

Kinsell found no elevation of serum cholesterol with the addition of cholesterol to the diet[112] Bronte Stewart added 3 grams of cholesterol a day to food mixtures without affecting the serum cholesterol[113] Ahrens *et al* showed that the addition of 2 grams per day of cholesterol produced no elevation in the serum cholesterol levels although the administration of 4 and 8 grams per day led to small but significant increases in cholesterol and phospholipid levels[114]

(B) *Quantity of Fat*

Diets low in fat are associated with a fall in serum cholesterol An example of this is the Kempner diet consisting of rice fruits and vegetables, which causes a lowering of blood cholesterol[115–118] Mellinkhoff *et al*[119] fed an artificial diet consisting of dextromaltose and egg-white hydrolysate with a resultant lowering of the blood cholesterol This suggests that it is not the lack of nitrogen that causes the cholesterol lowering effect of the Kempner diet

(C) *Quality of Fat*

Kinsell in 1952 showed that diets high in vegetable fats caused a marked decrease in the serum cholesterol and phospholipid levels, while the substitution of isocaloric amounts of animal fats caused a rise in these levels[120] Groen, also in 1952, showed that a diet containing 97 grams of vegetable fat a day caused a lowering of the serum cholesterol even though the total fat intake was high[121] Others confirmed the influence of "vegetable and "animal" fats on the serum lipid levels[122–126] However, not all vegetable oils lowered serum cholesterol, and not all animal oils raised it

It has become apparent that changes in serum lipids and cholesterol are

dependent on the degree of saturation or unsaturation of the fats rather than on their source. The highly saturated fats, such as butter, coconut oil and cocoa butter produce high levels of serum cholesterol, while diets with iso caloric amounts of highly unsaturated oils, such as safflower oil, corn oil and cotton seed oil, produce lower levels of cholesterol.

While most animal fats are rich in saturated fatty acids some (*i e* fish oils) have a high degree of unsaturation. Most vegetable oils are rich in unsaturated fatty acids but some (*e g* coconut oil) are high in saturated fats. The composition of the animal fat varies with the animal's diet and with the season of the year. That of vegetable oils varies with the variety of the product and the methods of its production. Thus the arbitrary division of fats into 'animal" and 'vegetable' is chemically meaningless.

Ahrens[127] reported a decrease in the phospholipid that paralleled the decrease in cholesterol. Nothman *et al*[128] and Shapiro[129] found that the phospholipid was not decreased proportionately with the cholesterol, so that the C/P ratio tended to be decreased following the ingestion of unsaturated fatty acids.

Ahrens found that the ratio of free to total cholesterol was unchanged with the drop in serum cholesterol. Shapiro *et al* found that the free fell to a greater degree than did the total cholesterol, while Nothman and his colleagues, and Kinsell found that the free cholesterol drop was slight in comparison with that of the esterified fraction. The reason for these differences is not clear.

In 1941 Snapper noted the great difference in the amount of unsaturated fatty acids in the diet of the Eastern and European civilizations.[130] Bronte-Stewart revived Snapper's hypothesis that especially the essential unsaturated fatty acids linoleic acid linolenic acid and arachidonic acid which are present in most oils but not butter, exert a depressing influence on the serum cholesterol. Bronte Stewart and his colleagues went on to show that when these poly unsaturated fatty acids were hydrogenated their favorable effect on serum cholesterol was lost and they now acted to elevate it just as did certain highly saturated fats such as butter and coconut oil.[131] This observation has been confirmed by others.[132,133] Keys has reported that the cholesterol raising effect of 1 gram of saturated fat can be offset by 2 to 3 grams of a high linoleic acid oil such as corn or cottonseed.[134]

Ahrens and his colleagues are inclined to the 'total unsaturated' theory as expressed by the iodine number. Keys and his colleagues[135] lean toward a balance between the 'saturated poly-unsaturated fatty acids with mono unsaturated fatty acids playing a neutral role." Kinsell[136] and Sinclair[137] are inclined to the concept of essential fatty acid deficiency.' However this theory is weakened by the fact that sardine oil, whale oil, and pilchard oil, which are exceedingly poor in essential fatty acids, but rich in other unsaturated fatty acids cause a lowering of the serum cholesterol, phospholipid and beta lipoprotein levels.[138,139,140] Ahrens *et al* and Malmros and his colleagues have shown that olive oil and rapeseed oil which consist of mono-unsaturated non-essential fatty acids also result in the depression of serum lipid levels.

Ahrens summarizes the theories as to the cause of the effectiveness of

the unsaturated fatty acids in lowering serum lipids as follows, "it is keenly debated today whether the effects described are due

(1) to the presence in all natural fats of trace elements (i e plants, sterols, vitamins, minerals) Beveridge suggested the effectiveness of corn oil is due largely to its beta sito-sterol content [141]

(2) to the absence in most oils of short and intermediate chain length fatty acids, (i e the C4–14) acids so richly distributed in coconut oil and butter Ahrens has shown that the ingestion of fatty acids shorter than C-16 may produce higher serum cholesterol and phospholipid levels than the C16 and C18 acids Butter which is rich in short and intermediate chain length acids, produces higher serum lipid levels than does cocoa butter which contains predominantly C16 and C18 acids, yet both fats contain the same amount of oleic and linoleic acids

(3) to the content of essential fatty acids in most natural fats and oils, (i e linoleic arachidonic, or others) or,

(4) to the aggregate unsaturation of the oil (i e the number of double bonds per unit weight of carbon)"

The mechanism by which the ingestion of poly-unsaturated fatty acids lower serum cholesterol has been reviewed by Proger He reports that it may be due to

(1) A more rapid metabolism of cholesterol
(2) A more rapid excretion of cholesterol
(3) A slower synthesis of cholesterol, or
(4) The sequestering of the cholesterol in some tissue other than serum [14]

Hellman *et al* [143] indicate by their studies that excretory mechanisms (increased excretion or decreased absorption) may explain the changes that are noted in serum levels of cholesterol as a result of the various types of fed fat Others also have observed that the fall in serum cholesterol following the ingestion of sunflower oil is due to the increased metabolism and excretion of cholesterol An increase in the rate of cholic acid secretion in patients with complete bile fistulae following the ingestion of sunflower oil by mouth and cotton seed oil intravenously also has been demonstrated This increase in the rate of cholic acid secretion preceded the fall in serum cholesterol Hydrogenated coconut oil did not affect the bile acid output but raised the serum cholesterol

In spite of the considerable evidence that the ingestion of poly-unsaturated fatty acids lowers serum cholesterol, some studies show that they are not uniformly effective in lowering serum cholesterol [144 145] It appears, at this time, that dietary restriction of animal fats and the ingestion of poly-unsaturated fatty acids are both important in the control of serum lipids

Effect of Heating Dietary Fats —It has been shown that heat results in polymerization of oils with the resultant production of toxic products In commercial food frying both heat polymerization and oxidative polymerization occur with resultant toxic products Witting *et al* [146] believes that these products exert their toxicity by destruction of pyridoxine and riboflavin and that the toxicity can be counteracted by supplementation of the diet with pyridoxine and riboflavin Melnick[147] questions whether commercial frying practices result in polymerization The changes which

that this type of sulpfur deficiency inhibited the production of taurine and hence of taurine-conjugated bile acids With the conversion of cholesterol to taurine-conjugated bile acids being limited by sulpfur deficiency in the diet, cholesterol accumulates in the plasma

Keys and Anderson[152] showed that increasing the intake of protein in man from a normal to a higher level did not result in any change in the serum cholesterol Olson *et al* [153] demonstrated that, with the calories, fat quantity and fat quality remaining constant a reduction of protein from 100 grams daily to 25 grams daily resulted in a fall in blood cholesterol within two weeks The reduction of dietary protein and choline, without altering dietary fat or calories, resulted in a hypo-beta lipoproteinemia as well The amino acids possibly involved in this effect were thought to be methionine (which appeared to be limiting), lysine, tryptophan, and *threonine (which were marginal)* The hypocholesterolemia did not parallel the degree of negative nitrogen balance and persisted as long as the low protein ration was fed Olson's studies support the important role of the liver in fat transport and suggest that dietary protein and choline may influence not only the liver fat content but also the concentration of the serum lipids and lipoproteins in the rat dog monkey and man

Scrimshaw *et al* [154] and Frenk and his colleagues[155] showed that the hypolipemia of kwashiorkor can be corrected by the administration of fat-free milk powder Hatch *et al* [156] demonstrated abnormalities in the bromsulfalein retention and in free to total cholesterol ratios in patients on the rice diet

(4) Dietary Carbohydrate and Serum Lipids

In 1919 Foster, Hooper and Whipple[157] noted that in dogs the excretion of bile acids was markedly reduced by feeding diets containing simple sugar Portman, in 1955,[158] showed that when dextrose or sucrose was substituted in the diet iso calorically for cornstarch, the total bile acid excretion decreased The findings suggested that the feeding of simple sugars affected the conversion of cholesterol to bile acids in some manner and the degree of experimental hypercholesterolemia might be related to the type of carbohydrate feeding Portman later showed[159] that cornstarch as a replacement for sucrose, glucose or fructose, resulted in lowering of the cholesterol levels The addition of sulfasuxidine to the diet to reduce the bacterial flora in the gut abolished the cholesterol lowering affect of starch In chickens, Grant and Fahrenbach[160] showed that cholesterol-induced hypercholesterolemia was greater with a sucrose than with a glucose diet

In man, Ahrens varied the proportion of fat and carbohydrate calories reciprocally, keeping total calories, protein and body weight constant Major changes were produced in the triglycerides, smaller effects in the phospholipids and least differences in the cholesterol The lowest serum lipid levels occurred on the highest intake of corn oil Ahrens noted no significant difference caused by iso-caloric exchanges of sucrose, dextrose and dextrins in his investigation of serum lipid levels in man

(5) Lipotropic Factors and Serum Lipids

Herrmann observed a decrease in total and cholesterol esters in the blood, aorta, heart muscle, and liver of chickens following the administration of choline.[161] Katz and Stamler found no influence of a diet containing inositol on the hypercholesterolemia induced in chickens by cholesterol feeding.[16] Morrison did not observe a choline effect on cholesterol level in man,[163] while Felch and his associates[164] observed a decrease in the hypercholesterolemia of patients who had sustained a myocardial infarction and in whom the blood cholesterol level, prior to choline administration, was 400 to 500 mgs. per cent. Greenberg and Bruger,[16] Jackson,[166] and Wilkinson[167] observed no influence on serum cholesterol or phospholipid levels following the ingestion of choline. Pomeranze and Chessin[168] observed no change in blood cholesterol level when a polysorbate-80-choline-inositol complex was given.

(6) Vitamin B and Serum Lipids

Nicotinic acid (niacin) in large doses lowers the serum cholesterol. Parsons[169] and Altschul[170] produced significant reductions in the blood cholesterol and total lipids with the ingestion of a high intake of nicotinic acid (1–6 Grams daily). Rivin reported[171] a decrease in the serum cholesterol levels, and relative concentration of beta lipoprotein in addition to a reduction in the size of xanthoma.

The physiologic mechanism by which nicotinic acid reduces the serum cholesterol is only partially understood. It is thought to have an effect on the enzyme systems of the liver which are involved in cholesterol synthesis and conversion to bile acids. This potential alteration in liver activity has led to liver function studies to rule out toxicity. Bromsulfalein tests and liver biopsies have failed to indicate toxicity.[169] A definite decrease in glucose tolerance with some glycosuria has been reported.[1] Rivin reported 1 case of jaundice occurring during the course of nicotinic acid therapy and possibly due to intra-hepatic cholestasis resulting from drug toxicity.[171] No other serious toxic side effects were noted in his series.

Pyridoxine Deficiency.—Experimental vascular lesions closely analogous to those of arteriosclerosis in man have been produced in monkeys fed a pyridoxine free diet for a period of 5 to 6 months. At the present time, however, there is no direct evidence that pyridoxine deficiency is a factor in atherogenesis in man.[171]

(7) Metals and Serum Lipids

(A) *Magnesium.*—A correlation of the serum magnesium and serum cholesterol in the South African Bantu and European subjects was reported in 1957. It was claimed that the higher the serum cholesterol level, the lower the serum magnesium.[173] These findings have not been confirmed.

(B) *Other Metals.*—Rosenman and Smith[174] studied the effect of certain chelating substances, ethylenediamine tetra acetic acid (EDTA) upon cholesterol metabolism in the rat. They showed that the oral administra-

tion of the chelating agent to the rat increased the dietary hypercholesterolemia by increasing intestinal absorption of cholesterol They found no effect on hepatic synthesis of cholesterol, and did not find that it protected against the deposition of fed cholesterol in the liver

(C) *Trace Elements* —Curran and Clute[175] showed that the *in vitro* conversion of acetate to cholesterol by liver cells was depressed by vanadium and iron, and increased by chromium and manganese The conversion of mavelonic acid to cholesterol was inhibited by vanadyl sulfate [176]

HUMAN ATHEROSCLEROSIS AND ISCHEMIC HEART DISEASE

Atherosclerosis is a disease of multiple etiology resulting from the interaction between endogenous and exogenous factors Olson has postulated that the interaction of the host and environment results in the production of the 'agent' of the disease [177]

TABLE 128 —ETIOLOGY OF HUMAN ATHEROSCLEROSIS

a) *Host*
  1) Heredity
  2) Race
  3) Age
  4) Sex
  5) Endocrines and metabolism
  6) Stress and strain
  7) Concomitant Disease (*i e* diabetes and hypertension)

b) *Environmental*
  1) Diet
  2) Drugs
  3) Exercise
  4) Occupation
  5) Climate

c) *Agent* (Arises from interaction of host and environment)
  1) Serum lipids
  2) Lipoprotein clearing factors
  3) Coagulability of blood
  4) Local factors that effect the response of the artery
    (*a*) Hemodynamic factors dealing with pressure and turbulence
    (*b*) Metabolic factors dealing with the arterial tissue itself with its structural composition and any trauma that it undergoes

The correlation between the amount or type of dietary fat, the concentration of serum lipids, and the incidence of ischemic heart disease, is accepted by some and questioned by others Evidence favoring this correlation has been presented in a large number of epidemiologic studies by Ancel Keys who has examined subjects in the United States, South Africa, Italy Spain, Japan and Hawaii [178] The validity of the conclusions drawn from the data on epidemiological studies has been questioned by Yudkin [179] Yerushalmy and Hilleboe,[180] and Mann [181]

Katz and Stamler[182] stressed the importance of coronary atherosclerosis as the keystone to the problem of ischemic heart disease Jolliffe[183] noted

that the differences in prevalence of coronary heart disease in various populations do not exactly parallel the degree or extent of atherosclerosis Becker,[184] and Lourie and Woods[185] found aortic atherosclerosis a common finding at autopsy among the Bantu Although aortic atherosclerosis is common in the Bantu coronary or ischemic heart disease as a cause of death is a rarity, while cerebral vascular complications are not much different than those in the European populations Some other factor, or factors must also be present to determine which of several individuals with approximately equal amounts of atherosclerosis are going to develop clinical coronary heart disease Among the additional factors thought to play a role are the chance strategic location of the atherosclerotic plaques, anatomic variations of the coronary vessels and abnormal intravascular clotting This last item includes increased blood coagulability and 'sludging," decreased fibrinolysis and changes in such other factors as lipid clearing and capillary fragility

In most countries of the Western World ischemic heart disease is the number one cause of death in men 30 years of age and older [186] Most of the reported increase unquestionably is factitious resulting from increased medical awareness and changes in reporting, however Lew reported a 15 per cent increase between 1940 and 1955 that cannot be accounted for by these factitious factors [187] By 1940 both awareness and clinical diagnostic facilities had been largely developed and disseminated throughout the entire medical profession The Lancet in an editorial also noted that there was a higher mortality rate from coronary heart disease due to a real increase in coronary artery disease and also that young people were affected more often than previously [188] The death rate from coronary heart disease is highest in the United States, and in the United States, it is highest in New York State and it is 10 per cent higher in New York City than in the rest of the state [189–191] In New York City, for men 50 to 59 years of age the death rate for arteriosclerotic heart disease in 1957 was 616 per 100 000

There is little doubt that real differences exist between the incidence of, and mortality from ischemic heart disease among the nations It is highest in the United States, Canada, Australia, New Zealand and Finland The mortality from ischemic heart disease in the Japanese the Bantu, in the Union of South Africa the Guatemalan Indians Nigerians, Yemmenite Jews in Israel Italians and Sardinians in Italy and low income men in Madrid, varies from one fourth to one-tenth of that in the United States Ad hoc surveys done in Japan Italy and South Africa[19 –195] help support the rough accuracy of statistical figures Teams of competent observers failed to find a prevalence of coronary heart disease comparable in any way to that found in this country Clinical and pathologic studies confirm the marked differences between countries and communities in the age-specific mortality rates for coronary heart disease [196 197]

In seeking the cause for the differences in the incidence of ischemic heart disease in different nations and in different groups in the nations it is essential to consider the multiple host and environmental factors previously noted

A HOST

(1) **Heredity**.—Certain families have a tendency for the development of coronary atherosclerosis and coronary thrombosis. Adlersberg and his associates[198] and Thannhauser and Magendantz[199] reported on the pre-disposition to the development of coronary artery disease in those patients with "forme fruste xanthomatosis." Groen and his associates[200] found considerable individual tolerance to high cholesterol diets. Some volunteers with a low blood cholesterol *did not show a rise in blood cholesterol*, even while on a diet rich in this material. Others with a high level at the onset of the test decreased somewhat on a completely vegetarian diet, but remained higher than normal. Experimentally, the same variation in reaction to cholesterol, has been reported. Most rabbits develop *hypercholesterolemia and atherosclerosis when fed diets high in cholesterol*, but the rise in cholesterol and the reaction of the arterial walls vary considerably. About 10 per cent of rabbits are entirely resistant to experimental atherosclerosis.

The relationship between body-build, serum lipids and atherosclerosis *has also been reported. Tanner*[201] *found a higher blood cholesterol level* in obese and athletic types than in tall, thin individuals. A similar correlation was found by Groen in his study. Spain and his colleagues[202] in a study of 157 cases of sudden death, found a strongly, positive correlation between the serum beta lipoprotein levels and the degree of atherosclerosis of the aorta *and coronary vessels at* post-mortem. The *correlation* was better among the endomorphs and mesomorphs than in the ectomorphs. Brouwer,[203] in Amsterdam, did not confirm these findings.

(2) **Race**.—The differences in incidence and severity of atherosclerosis which exist among people correlate with nutritional and dietary differences *rather than with racial differences*. Wilens[204] *reported that the inhabitants* of Costa Rica showed few or no atheromatous plaques in the aorta, coronary or other vessels. The diet in this country is low in animal protein, and fat. Steiner and Benjamin showed the amazingly low incidence of degenerative disease in autopsies done on Okinawans. The diet of Okinawans is predominently vegetarian, being high *in carbohydrate and low in fat*. *Oppenheim*[205] and Rosenthal[206] and Snapper have shown that atherosclerosis is rare in the Chinese. Collumbine[207] reported a low death rate from cardiovascular disease in Ceylon. Negroes in the United States are frequent victims of atherosclerosis, whereas negroes in Central Africa suffer infrequently from atherosclerosis.[208,209] In Israel, coronary thrombosis is found frequently amongst Jews from Western Europe and the United States, while it is almost unknown amongst Jews from the Near East, especially Yemenites.[210] Keys found a difference in the incidence of cardiovascular disease between the rich and poor classes in Bologna and Naples. Differences in the serum cholesterol levels and the incidence of atherosclerosis in the high and low socio-economic groups in India were related to the dietary intake of fat, rather than to race.[211] Katz quotes Kuczynski as recording a high incidence of extensive premature atherosclerosis in the nomadic Kirghiz plainsmen, whose diet consisted of large amounts of milk

and meat Their kinsmen, who had been urbanized and subsisted on a more varied diet did not exhibit such severe vascular disease

(3) **Age** —Keys and his colleagues demonstrated a definite relationship between serum cholesterol concentration and age in clinically normal men of 17 to 78 years of age [1] They found that the cholesterol levels increased to a maximum in the sixth decade and slowly declined thereafter These changes have been confirmed by the work of Barr and his associates and by Adlersberg and his colleagues [13] [14] Similar increases with age in the beta lipoprotein levels of the serum have been shown by Adlersberg Studies done on the South African Bantu [15] showed the same tendency of mean cholesterol values to increase with age as was observed in the Minnesota group However the tendency of the cholesterol to rise in the various age groups appeared to stop at the age of 40 in the Bantus There was no significant difference between the mean values obtained from the Bantus and Minnesotans up to this age group The failure to rise after the age of 40 was thought to be due to the habitual intake of a low fat diet Similar findings were noted in Spain and Italy where the diets also contain a low fat content

Gertler *et al* found that the rise in plasma cholesterol level with age occurred in a healthy group as well as in a coronary disease group [16] At every age level between the third and sixth decade, the coronary disease group had markedly higher serum cholesterol levels than the healthy group Gofman and his colleagues [17] found similar patterns of lipoproteins with low levels of Sf 12 to 20 lipoproteins up to 25 years of age The male population from 25 to 30 showed an increase in the Sf 12 to 20 level from 28 mgs per cent to 39 mgs per cent Beyond 30 years of age the clinically normal male population showed no further significant change, even through the 60th year The normal female does not show the striking change from 26 to 30 years of age that is seen in the male The female rises slowly and steadily in the Sf 12 to 20 level over the entire 25 to 60 year span, attaining the level attained by the male population of 30 years of age during the sixth decade

The explanation for the fall in serum cholesterol beyond the sixth or seventh decade is not clear It has been suggested that the apparent decline is the result of deletion from the population of those who might have succumbed to atherosclerotic coronary artery disease Another explanation for the lowering of the cholesterol beyond the age of 60, is the tendency of many elderly Americans to modify their dietary habits voluntarily, or involuntarily

(4) **Sex** —There is a lower incidence and less rapid development of atherosclerotic heart disease in the female as compared with the male [18] Adlersberg and his colleagues[219] reported 'the period of marked increase of serum lipid levels which occur physiologically in both sexes starts 13 years later in women than in men and lasts 12 years longer Russ Eder and Barr showed that the serums of young women had less beta-liproprotein and relatively more alpha lipoprotein than those of women of greater age or men of equal age Glazier and his colleagues [0] noted that the mean values of the beta-lipoprotein concentration in the serum was significantly higher in males than in females from the third through the

fifth decade They became approximately equal in the two sexes around the sixth decade and thereafter the mean value tended to be greater in women than in men This correlates well with the findings of the serum cholesterol values [1]

Following bilateral oophorectomy the degree of coronary sclerosis was found to be more severe than in a control group of women of comparable ages Reduction of the serum lipid levels, as reflected by the total serum cholesterol and serum beta-lipoprotein concentration has been effected in male survivors of myocardial infarction by the use of estrogen therapy [23] Testosterone has resulted in an elevation of the beta-lipoprotein levels in the serum of male survivors of myocardial infarction [224]

Block *et al* [25] reported that following a standard fat meal, men develop a significantly greater plasma lactescence than women of the same age group They suggested that this may be of significance for atherosclerosis

(5) **Endocrines and Metabolism** —(*a*) *Adrenal-pituitary* —Hyper-adrenocorticism, as in Cushing's syndrome, is associated with severe atherosclerosis [6] Adlersberg reported a rise in plasma lipids, including cholesterol in patients receiving cortisone [2 7] Less consistent changes have been obtained with ACTH administration

(*b*) *Thyroid* —Plasma cholesterol levels, as well as the plasma lipids, tend to be elevated in hypothyroidism or myxedema [8] Marked athero sclerosis has been reported in Cretins [9, 30, 231] It is difficult to correlate these findings with the reports that coronary thrombosis is not more fre quent in such patients [23] Hyperthyroidism, on the other hand, is associated with a very low incidence of coronary atherosclerosis and myocardial infarction [33]

(*c*) *Diabetes* —The incidence and severity of coronary atherosclerosis is greater and more frequent among diabetics than among non diabetics [234] Diabetes mellitus is the most important clinical entity associated with disturbed lipid metabolism and a hypercholesterolemic tendency "The universality of atherosclerosis in diabetes" is true for young and old, female and male [23] Diabetes eliminates the relative immunity of women to atherogenesis [36] Young diabetics develop "degenerative" vascular disease at an early age [237]

The plasma lipids were markedly *elevated in the pre-insulin era in the* diabetic of long standing with frequent episodes of ketosis There is a difference of opinion as to the effect of "control" on the serum lipids Some claim that *with adequate treatment, a normal plasma lipid pattern* may be obtained [238, 39, 240] Pomeranze and Kunkel, on the other hand, found no relation between degree of diabetes control and plasma lipids [41] They *found a close correlation* between hyperlipemia and atherogenesis in 273 diabetics Fifty per cent exhibited elevated serum lipid levels irrespective of diabetes control Seventy-two per cent of those with severe atherosclerosis had hyperlipemia, with some abnormality found in 90 per cent on complete fractionation Gofman has demonstrated high concentrations of Sf 10 to 20 class in diabetic males and females

Groen claims that atherosclerosis is more severe in diabetics in the United States than in those in Europe He associates this with the high fat diet in the United States He studied the diet and atherogenesis in Trappist

monks These monks live on a strictly vegetarian diet low in fat Diabetes is not rare in the older monks These diabetics who have been on a vegetable diet, poor in fat, have low cholesterol levels and atherosclerosis seems to be less frequent among them The same low incidence applies to the non diabetic monks when compared to the population at large Groen feels that both the disturbance in metabolism and the diet, play a role in the increased incidence of atherosclerosis in the diabetic

(6) **Stress and Strain** —The relationship of stress with coronary artery disease was noted by Osler in 1899[4] and again by Stewart in 1950[243] A considerable difference in the type of civil positions held by young coronary patients when compared with controls has been reported[44 45] The young coronary patients had a higher incidence of positions demanding responsibility and frequently associated with emotional stress Brock and Bronte-Stewart pointed out that job responsibility correlated well with the increased incidence of ischemic heart disease[46] Friedman and Rosenman also reported the inter-relationship between emotional stress hypercholesterolemia, clotting and clinical coronary artery disease[17] The effects of stress were measured in a group of 42 volunteer accountants This group was selected because of the unusual phasic variations of their work In 83 per cent of the subjects the maximum cholesterol determination occurred at the time of the maximum stress as measured by nearness to income tax dead lines Blood clotting time was shortened from an average of 9 4 minutes during minimal stress to 5 minutes at the time of maximal stress The authors could not ascribe the changes in the blood cholesterol or clotting mechanism to diet or changes in weight In their most recent investigation they extended their observations by selecting subjects according to degrees of stress and found highest serum cholesterol levels in the subjects most stressed as measured by their criteria

(7) **Concomitant Diseases** —There is a higher prevalence of ischemic heart disease in individuals with diabetes mellitus myxedema, nephrosis and the lipodystrophies, in which hypercholesterolemia is a common factor than in normals

(a) **Familial Hypercholesterolemia, or Familial Xanthomatosis,** is a syndrome which consists of xanthelasma, arcus senilis xanthoma tuberosum xanthoma tendinosum hypercholesterolemia and coronary artery disease It is associated with an increase in total serum cholesterol a slight rise in phospholipids, little or no alteration in neutral fat, a normal ratio of free to total cholesterol, and an elevated ratio of total cholesterol and free cholesterol to phospholipid Markedly elevated levels of Sf 10 to 20 lipoproteins are present Adlersberg[48] *et al*, and others[49 50 51] demonstrated conclusively that the hypercholesterolemia of familial xanthomatosis is associated with a high incidence and early onset of ischemic heart disease

(b) **Nephrotic Syndrome** —The plasma cholesterol and other lipids are markedly elevated in the nephrotic syndrome There is usually a rise in the plasma phospholipid which parallels the hypercholesterolemia so that the C/P ratio is not altered much The neutral fat also rises as does the Sf 10 to 20 class of lipoproteins From the available data it appears that the hypercholesterolemia of renal disease is associated with intensified atherogenesis

(*c*) **Biliary Disease** —Ahrens and Kunkel report a lack of correlation between the elevated serum levels of cholesterol and intensified atherogenesis in obstructive biliary disease They relate this lack of correlation to the normal C/P ratios obtained Others have found increased atherogenesis in those cases of biliary obstruction in which there was hypercholesterolemia and elevated plasma C/P ratios

(*d*) **Hypertension** —The relationship between hypertension and atherosclerosis is a complex one Most investigators agree that while hypertension promotes atherosclerosis, there is no correlation between the degree of hypertension and the severity of the atherosclerotic lesions [253]

B ENVIRONMENTAL FACTORS

1) **Diet** —The relationship between dietary factors and serum lipids has been discussed above The following section will relate dietary factors to atherosclerosis and ischemic heart disease

(*A*) *Total Calories* —In the United States, insurance statistics suggest that obesity either causes or speeds up the development of ischemic heart disease[254] French and Dock[55] found that most of a group of 80 young soldiers who died of a coronary attack were overweight However, Yater and his colleagues[56] found that obesity was not a significant finding in 233 young soldiers who died of coronary attacks when compared with 297 men of the same age group, 18 to 39, who died as a result of accidents The groups studied by Yater included the 80 soldiers reported by French and Dock Garns Gertler *et al* [7] *also were unable to correlate obesity with* myocardial infarction Dawber, Moore and Mann, however, in the Framingham study reported that obesity, as well as hypertension and hypercholesterolemia, favored the development of ischemic heart disease

The effect of calorie excess and obesity on hypercholesterolemia, atherosclerosis and ischemic heart disease remains to be clarified There also is a difference of opinion amongst pathologists as to whether obesity contributes to atherosclerosis found at autopsy Wilens'[8] found that advanced atherosclerosis was more common in the obese while Faber and Lund[259] found that obesity had no effect on atherosclerosis when hypertension was taken into account Experimental atherosclerosis can be produced in animals by excess calorie feeding[60]

(*B*) *Fat Intake and Atherosclerosis and Ischemic Heart Disease* —Keys and his colleagues have held that fat intake rather than total calories is correlated with death rates from heart and blood vessel disease in various countries Keys and White expressed the relationship between the total fat intake and coronary heart disease rates for males below 65 as follows "Populations with fat intakes approximating 40 per cent of the total calories have high coronary death rates, populations with total fat intakes below 20 per cent of the total calories have low death rates, populations with intermediate fat intake have intermediate death rates

Jolliffe and Archer[61] and others have shown, in a comparison of multiple environmental factors in the etiology of death rates from coronary heart disease, that the intake of saturated types of fat was most important in accounting for the differences in coronary heart disease death rates between countries

TABLE 129.—DEATH RATES FOR MEN AGED 55 TO 59 YEARS AND ENVIRONMENTAL FACTO[RS IN] 20 COUNTRIES (Jolliffe and Archer.)

Country	*Death rate per 100 000* (A)	(B)	(C)	(D)	*Average Total daily calories* (E)	*Component as per cent of total calories* (F)	(G)	(H)	(J)	*Telephones per 100 population* (K)
United States	704.7	660	979.7	1,830	3 070	39.2	33.5	5.7	8.2	3[illegible]
Australia	577.4	516	802.6	1 690	3 160	37.9	34.7	3.2	7.3	1[illegible]
Austria	293.9		545.4	1 780	2 820	31.3	23.9	7.4	5.8	[illegible]
Belgium	250.1		473.3	1 720	2 980	35.0	24.4	10.6	5.7	1[illegible]
Canada	588.3	550	790.8	1 510	3 130	38.0	35.0	3.0	8.0	2[illegible]
Ceylon	103.4		233.9	1 350	1 980	15.2	11.8	3.4	2.2	[illegible]
Chile	267.3		569.5	2 440	2 490	19.8	12.0	7.8	4.3	[illegible]
Denmark	294.8	260	484.9	1 180	3 370	38.3	25.5	12.8	6.1	2[illegible]
Finland	621.7	483	907.6	2 040	3 170	31.1	28.4	2.7	6.8	1[illegible]
France	109.9	106	435.0	1 760	2 850	29.5	20.7	8.8	6.4	[illegible]
German Federation	313.7	194	502.0	1 570	2 950	35.6	23.0	12.6	5.6	[illegible]
Italy	226.8	120	459.9	1 450	2 550	22.3	10.5	11.8	3.6	[illegible]
Japan	122.5	50	612.2	1 810	2 005	7.9	1.4	6.5	2.6	[illegible]
New Zealand	525.7	492	726.8	1 410	3 370	39.8	37.6	2.2	8.2	2[illegible]
Norway	248.8	210	390.5	1 050	3 130	38.0	17.0	21.0	6.4	1[illegible]
Portugal	107.7		495.6	1,630	2 560	24.5	9.4	15.1	3.9	[illegible]
Sweden	294.6	216	473.0	1 110	3 070	39.4	38.3	11.1	7.3	3[illegible]
Switzerland	273.0	173	474.2	1 [illegible]10	3 100	33.6	23.6	10.0	6.6	2[illegible]
United Kingdom	427.5	371	651.8	1 700	3 270	38.4	35.0	3.4	5.9	1[illegible]
Yugoslavia	68.2		149.6	1 800	2 525	19.1	13.2	5.9	2.8	1[illegible]

(*A*) ISC category B-26 (arteriosclerotic and degenerative heart disease). Values actually [used] in the correlations were the logarithms of the numbers in this column.
(*B*) ISC category 420 (arteriosclerotic heart disease).
(*C*) Combined ISC categories B 22 (vascular lesions affecting the central nervous system), (chronic rheumatic heart disease), B-26 (arteriosclerotic and degenerative heart disease), (other diseases of the heart), and B 28 (hypertension with mention of heart disease).
(*D*) Total death rates.
(*E*) Average total available daily calories. FAO.
(*F*) Total fat intake.
(*G*) Saturated types of fat intake.
(*H*) Unsaturated types of fat intake.
(*J*) Animal protein intake.
(*K*) Telephones per 100 population.

Another major factor contributing to the change of fat quality is "hydrogenation," a process by which oils such as cottonseed and soy bean oil are changed into solid fats. Hydrogenation results in four major changes in the fat.

(1) Production of saturated from unsaturated fatty acids or decreasing the number of double bonds and polyunsaturated acids as indicated by lowering of the iodine number.

(2) The double bond may shift in position producing iso acid forms. These new unsaturated acids may have the same iodine number but may differ from the original in melting point.

(3) The predominantly occurring "cis" configuration may change to the "trans" configuration, and

(4) With linoleic, linolenic, or arachidonic acids there may be conjugation

As a result of these changes the fat may become solid at ordinary room temperature with an iodine value of that of olive oil The linoleic acid content has been reduced from around 50 per cent originally to 3 to 8 per cent after hydrogenation

(*C*) *Protein* —Olson has stressed the importance of the dietary intake of protein in hypercholesterolemia and atherosclerosis Jolliffe and Archer confirmed the relationship between dietary protein and ischemic heart disease Experimentally, Newburg and Clarkson [6] found that feeding rabbits a diet containing 36 per cent protein resulted in atherosclerosis sooner than in those rabbits that received only 27 per cent protein The extent of the atherosclerosis was proportional to the duration of the feeding

(*D*) *Carbohydrate* —Yudkin [63] reported that incidence of ischemic heart disease showed a better relationship to the intake of sugar than to any other major foodstuff

(2) **Drugs** —(*A*) *Tobacco* —There is a high association between cigarette smoking and the incidence of coronary artery disease Hammon and Horn, in their study of nearly 200 000 people in the United States showed a higher frequency of coronary thrombosis among cigarette smokers than among cigar smokers, pipe smokers and non-smokers [64] The death rate from coronary artery disease was 75 per cent higher among cigarette smokers than among comparable group of men who never smoked Moreover, the death rates due to coronary artery disease increased with the amount of cigarette smoking A similar pattern was observed in physicians in England [65] Although there is the parallel positive correlation between cigarette smoking and the development of coronary thrombosis, there is no proof of causal relationship

(*B*) *Alcohol* —It has been noted clinically that atherosclerosis and ischemic heart disease are uncommon in alcoholics Mortality from coronary thrombosis is low in certain districts of France where alcohol consumption is high Wilens confirmed the low frequency of atherosclerosis in alcoholics and attributed it partially to the fact that alcoholics often die at an early age and partially to the fact that hypertension is less common among them [66] The abnormal diet of alcoholics may play as great a role in the causal relationship as the alcohol intake itself

(3) **Exercise** —The incidence of atherosclerotic heart disease is lower in those who exercise than in those who live a more sedentary life Morris *et al*[267] found a greater mortality from coronary heart disease in bus drivers than in conductors He felt that two factors were responsible, the increased physical activity of the conductors, and the increased emotional tension of the drivers while driving through city traffic He also found a lower incidence of coronary heart disease in mailmen Biorck and his associates in Malmo, Sweden, found a lower frequency of myocardial infarction among laborers than in people living a sedentary life [68] Keys *et al* found a lower blood cholesterol level among metal workers than among firemen and office workers Ingestion of a diet of 6,000 calories a day in 3 men, had no influence on plasma cholesterol, phospholipids, and lipoprotein when

physical exercise was great enough to utilize these calories When exercise was decreased so that fat was deposited, two men showed an increase in serum lipid levels Mann and his colleagues,[69] and Yudkin[270] also have stressed the importance of physical activity in the etiology of atherosclerosis and ischemic heart disease

(4) **Climate** —There is no relationship between climate and the serum lipid level or atherosclerosis Florida and Maine have similar adjusted death rates from coronary heart disease while West Virginia and Maryland and Mississippi and Louisiana, which have essentially the same climate, have marked differences in the incidence of coronary heart disease

C AGENT

Arising from the inter action of the host and environmental factors is the "agent"

(1) **Serum Lipids** —The relationship of serum cholesterol the cholesterol phospholipid ratio, alpha and beta lipoproteins and Sf 10 to 400 lipoproteins to atherosclerosis has been discussed above

(2) **Lipoprotein Clearing Factor** —Hahn [271] and Anderson and Fawcett[272] discovered a humoral factor able to clear lipemic serum Injection of a small amount of heparin, 5 to 20 milligrams into man after a meal rich in fat, caused immediate clearing of the lipemic plasma Heparin *in vitro* does not result in the clearing of lipemic plasma however plasma from a person injected with heparin can clear lipemic plasma *in vitro* It thus appears that heparin releases a "clearing factor which circulates in the plasma

An enzyme, lipoprotein lipase recently has been isolated from the rat heart It is found in highest concentration in the heart (but also in liver kidney, lung and spleen) It is activated by heparin and its release into the blood stream from cardiac tissue is stimulated by the administration of heparin Under suitable circumstances it can reduce, *in vitro*, the turbidity of lipemic sera the same as does 'post-heparin plasma [27 74]

Fat emulsions given intravenously daily have been found to cause a fall in the serum cholesterol phospholipid and triglyceride levels It is believed that the infused fat and that which disappears from the blood stream are both rapidly metabolized [275] There is also an increase in the electrophoretic mobilities of the serum lipoproteins following fat infusions The same effects have been noted after heparin injections and it is postulated that the infusion of fat may trigger the relea e of clearing factor

The relationship of post-cibal lactescence to the gradual development of atherosclerosis is undetermined at this time Following a fat rich meal the cloudy serum contains no more cholesterol than clear serum The smaller particles which contain cholesterol are efficiently phagocytosed by the reticuloendothelial system while the larger ones which consist mainly of neutral fats are held in the blood disappearing only gradually The cholesterol level in cloudy plasma does not change when the 'clearing' factor is added *in vitro*, but the size of the particles that contain fat and cholesterol does change under the influence of an enzyme that separates

the protein from the lipids.[76] It is uncertain whether the "clearing" factor plays any role in the pathogenesis of atherosclerosis.

(3) **Coagulability of the Blood.**—The coagulability of the blood is significantly shortened after a high fat meal, and it has been suggested that this could account for the high incidence of coronary thrombosis in hyperlipemic states.[77, 78] Poole *et al.* showed that the phosphatide in chylomicrons was responsible for the increased clotting time of recalcified citrated plasma.[279] The active principle was identified as phosphatidyl ethanolamine. O'Brien[280] confirmed the observation that phosphatidyl ethanolamine, in small concentrations, activated clotting *in vitro*. He reported extreme coagulability, with marked acceleration of the Stypven time, following the ingestion of butter and margarine, but especially after egg yolk.

O'Brien[81] *found no difference in Stypven clotting times after fat meals* in 20 male patients with coronary thrombosis as compared with 20 aged matched male volunteers. However, MacDonald and Edgill,[82] studying 48 patients in each group, found statistical differences in a number of clotting indices. It was not possible to predict thrombotic tendencies in any *given patient and it was impossible to determine whether the increased* coagulability in the coronary patients was cause or effect of the disease.

Ahrens stresses the need for further investigation to determine (1) the reason for the extreme hypercoagulability of blood after meals containing eggs, (2) the site of action of specific phosphatids in the complex chain of events which is termed "clotting," and (3) the relationship between clotting activity as measured outside the body and the phenomenon of thrombosis itself.

Fibrinolysis.—Fibrin strands are being continually deposited on the vascular endothelium, and are being removed by fibrinolysis. Inhibition of lysis could lead to the same effects as *increased coagulation.*

Greig[83] showed that the ingestion of a high fat meal causes an inhibition of fibrinolysis corresponding to the degree of hyperlipemia. Cream added to non-lipemic plasma causes an inhibition of fibrinolysis. Heparin administered to subjects with a lipemic plasma restores fibrinolytic activity to normal. Inhibition of *in vitro* fibrinolysis after a fat meal is decreased by exercise. Butter, eggs and bacon cause a marked inhibition of fibrinolysis, while all vegetable oils, regardless of degree of unsaturation, activate fibrinolysis.

Blood Viscosity.—Watson found no alteration in blood viscosity following a fat meal[284] while Swank *reported increased* adhesiveness, and (aggregation) and a decreased sedimentation rate.[85] The accumulation of chylomicrons 6 to 9 hours after a fat meal was less following the ingestion of unsaturated fats than following saturated fats.

Capillary Fragility.—Capillary hemorrhages may be a factor in accelerating atherosclerosis but their relationship to dietary lipids is not known. An essential fatty acid deficiency in rats causes increased capillary permeability.[86]

SUMMARY OF PATHOGENESIS OF HUMAN ISCHEMIC HEART DISEASE

Susceptibility is mediated by such host factors as heredity, race, age, sex, endocrine status, and concomitant disease, and the environmental factors

of diet, drugs, exercise, occupation, stress and strain. Many investigators feel that the major factor in the etiology and pathogenesis of ischemic heart disease is the high intake of saturated and hydrogenated fats, and the other factors play but a minor role. A high intake of poly-unsaturated fatty acids, as well as a low intake of saturated fats, is thought to be important in reducing the high rate of coronary heart disease. This is not universally accepted since some feel that exercise is at least as important as any other factor.

Admittedly, there are many non susceptible people who can tolerate large quantities of saturated fats over a long period of time; however there is no way of recognizing or predicting these people in advance.

DIET IN MANAGEMENT OF ATHEROSCLEROSIS

Even though there is no proof that a change in the diet will prevent coronary (ischemic) heart disease or coronary occlusion or a cerebral vascular accident, there is sufficient data indicating a relationship between lipid metabolism and atherosclerosis to warrant certain changes in our dietary habits.

According to Ahrens:

(1) Substitution of dietary fats rich in poly unsaturated fatty acids fc those rich in saturated fatty acids will lower cholesterol levels : almost every person whether normocholesterolemic or hype cholesterolemic.

(2) The greater the substitution the greater the effect. (At least 75 per cent of the calories derived from fat must be of the poly-unsaturated type and the proportion of calories from fat in the total caloric intake must be 40 per cent.)

(3) The effects are due to the fatty acid structure and not to trace factors.

(4) The effects are due to the poly unsaturated fats and not to the correction of an essential fatty acid deficiency.

(5) Sitosterol and nicotinic acid decrease serum cholesterol by other mechanisms.

Shapiro, Estes and Hilderman[87] showed that when 70 per cent of fat intake was made up by corn oil and the total fat restricted to 100 grams per day, impressive depressions of all serum lipid fractions occurred. All the fractions tested except beta lipoprotein and iodine numbers tended to return toward control values when the calories and total fat intakes were increased and the per cent of total fat made up by corn oil was reduced to 41 per cent. Meltzer, Bochman and Berryman[88] studied the effect of a pharmaceutical emulsion of safflower oil plus sitosterol plus pyridoxine plus Vitamin E on the blood cholesterol level of 28 patients aged 36 to 53 with hypercholesterolemia and myocardial infarction. With the patients maintaining their previous diet plus the dietary supplement for six months there was a significant decline in serum cholesterol levels for all ten patients consuming less than 50 grams of dietary fat daily, for seven to eight patients consuming 50 to 100 grams of dietary fat daily and for seven of ten consuming 100 to 150 grams of dietary fat daily. Gordon and Brock[289] also were able to affect a significant fall in the serum cholesterol

level in eight to ten subjects within six months by the feeding of sunflower seed oil as a supplement to the regular diet Perkins, Wright and Gatje,[90] however, reported no significant effect on the serum cholesterol when an emulsion containing 48 cc of safflower oil was added daily to the regular diet of 24 medical students aged 22 to 26 for six to seven weeks McCann and her associates[91] fed eight ounces of a peanut oil emulsion containing 960 calories and supplying 36 per cent peanut oil and 4 per cent coconut oil to a group of 20 faculty members aged 37 to 65 In order to keep weight constant the omission of some of the ordinary food, usually the visible fat, was necessary Twelve of the 20 persons showed a fall in serum cholesterol of more than 10 per cent from the original level Later, 10 of the original 20 men completed a further four weeks study in which they took three tablespoonsful daily of a 50 per cent safflower oil emulsion Of these ten men, six showed a decrease of 10 per cent or more in serum cholesterol levels

Tobian, and Tuna[292] studied 23 patients with coronary atherosclerosis with an average blood cholesterol of 271 mgm per cent Their patients were instructed to ingest one to one and one-half ounces of corn oil before each meal and to use corn oil in the preparation of food Eighteen of these patients were instructed "to avoid butter fat, margarine, various hydrogenated vegetable oil preparations, and more than one egg a day The other 5 were given no dietary restrictions The drop in cholesterol was significant in both groups and maintained over a period of one year

Jolliffe and his group[93] found the average cholesterol level of 79 men of normal weight, age 50 to 59, to be 251 mgm per cent When distributed into previously established tertiles on the basis of their cholesterol levels, 28 men fell in the highest third, (279 mgm per cent and over), 24 in the middle, and 27 in the lowest third, (under 230 mgm per cent) They were placed on a diet of 2000 to 2700 calories with fats 66 to 97 grams (30 to 33 per cent of the calories), protein 130 to 150 grams, and carbohydrate 225 to 280 grams Predominantly saturated types of fat were limited to not more than 15 per cent of total calories, yielding 7 to 8 per cent of the total calories as saturated fatty acids The balance of fat, up to a total of 33 per cent of total calories was derived from unsaturated types consisting of one to one and one-half ounces of corn oil, or its equivalent, and fats from fish grain and vegetables with total amount of polyunsaturated fatty acids comprising 9 to 11 per cent of total calories After six months on the diet the group cholesterol average fell from 251 to 222 mgm per cent By tertile the levels fell from initial averages of 298, 250 and 204 to 252, 225 and 189 mgm per cent respectively Control weights averaged 154 pounds after six months on the diet the average was 153 pounds This study demonstrates that the serum cholesterol level of a group of subjects can be significantly lowered (although not necessarily optimally) by adherence to a diet containing 9 to 11 per cent of total calories as polyunsaturated fatty acids, with the saturated fatty acids component comprising seven to eight per cent of total calories Of 86 men placed on this diet originally, 79 (92 per cent) continued for at least six months indicating a wide acceptance among this group of motivated subjects Jolliffe *et al* concluded that (1) a prudent diet is practical and can be

followed by the vast majority of sufficiently motivated subjects for at least six months, and (2) that this diet significantly lowers the average blood cholesterol level over a period of six months

DIETARY PATTERN FOR UNSATURATED FATTY ACIDS UP TO 33 PER CENT OF TOTAL CALORIES IN THE DIET

Food	*Amount*
Milk	
Skim	
Whole	In coffee only
Egg	Maximum 4 weekly (The white of eggs not restricted)
Meat, Poultry (See below)	
Leaner group	5 times weekly
Fattier group	Maximum 24 oz weekly
Fish	At least 5 times weekly *Use Freely*— salmon sardines tuna mackerel white fish herring shad
Cheese	
Cottage, pot, farmer	
Bread and Cereals	
Enriched or whole grain	
Vegetables	
Potato white sweet	
Leafy, green yellow	
Other vegetables	
Eat raw vegetables frequently	
Fruits	
Citrus	
Other	
Corn Oil	1 oz (2 tablespoons) DAILY or equivalent

Foods Not Restricted
Foods that have nutrients
- Fruits and vegetables
- Skim milk
- Bread and cereal
- Nuts

Foods that have calories only
- Jello
- Water ice
- Sherbet
- Angel food cake
- Hard candy
- Liquor wine beer

MEATS FOWL FISH CHEESE

LEANER GROUP

Meats	*Fowl*
Veal	Chicken
Liver	Turkey
Kidney	

FATTIER GROUP (Leaner cuts)

Meats
- Beef
  - Round
  - Rump
  - Sirloin
- Tongue
- Lamb
  - Leg roast
- Pork
  - Ham steak
  - Sirloin roast
  - Ham butt-end
  - Canadian bacon

Foul
- Duck

FISH

Fish

Bass	Halibut	Shad roe
Blue fish	Herring fresh, pickled, *etc*	Shrimps
Bonita	Lobster	Sturgeon
Butterfish	Mackerel	Sword fish
Clams	Mussels	Trout
Cod	Oysters	Tuna fresh, canned
Crabmeat	Pike	Weakfish
Eels	Salmon, fresh, canned, smoked	Whitefish
Finnan haddie	Sardines	and other fish
Flounder	Scallops	
Haddock	Shad	

CHEESE

Pot	Cottage	Farmer

Do Not Eat

Meats
- Ham and Pork Products (Other than those allowed)
- Bacon
- Sausages
- Luncheon meats, salami, pastrami
- Corned beef

Dairy Products
- Whole milk
- Butter
- Margarine
- Cream cheese
- Ice cream
- Sweet and sour cream
- Hard type cheese

Desserts
- Cakes
- Pies
- Cookies
- Doughnuts
- Muffins
- Fancy crackers
- Puddings

Except those baked at home with corn oil or equivalent

Miscellaneous
- Salad dressing
- Chinese foods
- Gravy
- Peanut butter
- Popcorn
- Potato chips
- Chocolate candy
- Fats and oils—other than corn oil or equivalent
- Fried foods—unless prepared at home with corn oil or equivalent

General Precaution
- In frying do not re-use corn oil or equivalent
- Do not let oil reach the smoking point

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Anti Coronary Club
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The various clinical forms of allergy may be classified according to the major systems of the body in which the sensitized tissue areas chiefly involved in the allergic response are found These major systems are (*a*) respiratory, (*b*) alimentary, (*c*) cutaneous, (*d*) neural, (*e*) cardiovascular, (*f*) genito-urinary, and (*g*) articular Since tissue areas in several major systems may be sensitized to the same antigen, several manifestations of clinical allergy may result in an individual from a single type of invading antigen In the individual sensitive to clams, for instance, the ingestion of his specific excitant may result simultaneously in coryza, bronchial asthma, pruritus, urticaria, tracheal edema, abdominal cramps and diarrhea, due to activity in various sensitized areas of the respiratory, cutaneous, and alimentary systems

TABLE 130 —THE CLINICAL FORMS OF ALLERGY

1 Skin sensitive or Wheal Type (Immediate Reaction Type)
- (*a*) Hereditary Spontaneous
  - Allergic coryza seasonal (hay fever), nonseasonal bronchial asthma
  - Causes Airborne, pollens dusts, fungi, foods
  - Urticaria angioedema of skin or alimentary tract, allergic headache allergic nerve disorder
  - Causes Foods
- (*b*) Nonhereditary Induced physiologic anaphylactic, serum sickness, therapeutic accidents
  - Causes Heterologous serum antibiotics insulin organ extracts, toxoids virus vaccines (egg media) helminths serum conjugates
- (*c*) Physical allergy Asthma urticaria angioedema purpura headaches
  - Causes Heat cold sunlight

2 Skin negative or Non wheal Type (Delayed Reaction Type)
- (*a*) Noninfective
  - Hereditary Allergic coryza bronchial asthma urticaria angioedema, dermatitis allergic headaches allergic nerve disorders
  - Causes Foods some drugs
  - Nonhereditary (1) Drug allergy, allergic coryza bronchial asthma urticaria angioedema dermatitis vascular allergy
  - Causes Aspirin, quinine sulfonamides, mercury serum conjugates
  - Nonhereditary (2) Contact dermatitis
  - Causes Natural and synthetic oils resins chemicals, drugs, foods
- (*b*) Infective
  - Hereditary Allergic coryza bronchial asthma urticaria angioedema of skin or alimentary tract dermatitis, sinusitis
  - Causes Bacterial and fungus products
  - Nonhereditary Tuberculin type sensitization, periarteritis vascular allergy, *rheumatoid arthritis*
  - Causes Bacterial products

Cooke [1] pointed out that the allergic response may be either of an immediate reaction type, occurring within four hours after contact with the antigen or a delayed type, requiring from four to seventy-two hours for the appearance of the symptoms Both types may be present in a single patient but to different excitants, a person may develop asthma immediately upon contact with horses, but urticaria only after a delay of twenty-four hours following the eating of egg Furthermore, a food antigen may

cause immediate symptoms in one patient, delayed in another While the length of the reaction time may vary from person to person and from cause to cause, it is always a constant in any one individual to any given antigen The immediate type is also termed the skin-sensitive, or wheal type, since the immediately positive skin test, with typical wheal formation may be obtained in sensitive individuals on application of the extract of the specific excitant by intracutaneous or scarification procedures The delayed reaction type is also designated as the skin-negative, non wheal type, due to its behavior upon skin test An attempt to classify the varieties of clinical allergy is shown in Table 131

TABLE 131 —CLASSIFICATION OF FOOD ALLERGY

1 Skin sensitive or Wheal Type (Immediate Reaction Type)
- Antibody Skin sensitizing
- A Hereditary Spontaneous abrupt obvious often severe symptoms involving all major systems of body
  - Portal of entry
  - (a) Alimentary mucosa
    - Causes Foods by ingestion
  - (b) Respiratory mucosa
    - Causes Inhaled dusty airborne food dusts and volatile food odors by inhalation (rare)
  - (c) Skin
    - Causes Foods by percutaneous absorption (rare)
  - (d) By parenteral injection
    - Causes Therapeutic agents containing food excitants
- B Nonhereditary Induced anaphylactic often severe symptoms involving all major systems of body
  - Portal of entry
  - By parenteral injection
    - Causes Sensitizers such as organ extracts virus vaccines (egg media)

2 Skin negative or Non wheal Type (Delayed Reaction Type)
- Antibody Unknown
- (a) Hereditary Deliberate obscure symptoms involving all major systems of the body
  - Portal of entry
  - Alimentary mucosa
    - Causes Foods by ingestion
- (b) Nonhereditary Induced (contact dermatitis) rare involving respiratory and cutaneous systems
  - Portal of entry
  - Intact oral and buccal mucosa and skin
    - Causes Foods essential oils of foods and spices

The Clinical Manifestations of Food Allergy —Food allergy may produce any of the various manifestations of sensitivity previously enumerated with the exception of pollenosis, which is always due to plant pollens, bacterial allergy and physical allergy It may be the sole or a contributing cause producing symptoms of the immediate or delayed type, acute or chronic mild or severe Sensitivity to foods may manifest itself in the respiratory system as coryza, conjunctivitis, bronchitis, bronchial asthma and sinusitis, in the alimentary system as manifestations of ... enteritis,

such as herpes, stomatitis, bad breath, "bilious" attacks, gingivitis, nausea, vomiting, flatus, abdominal distention and pain, colitis, diarrhea, constipation, pruritus ani, and in the cutaneous system as pruritus, dermatitis, urticaria, angio-edema, purpura, in the neural system as headache, peripheral neuritis, optic neuritis, vertigo, allergic labyrinthitis, in the cardiovascular system as tachycardia, in the genito-urinary system as hematuria, pruritus vulvæ in the articular system as arthralgia, in the ocular system as conjunctivitis, corneal ulcers It must be emphasized that food sensitivity is only an occasional or rare cause of many of these manifestations The symptoms of food allergy may mimic those of many other clinical conditions It is often difficult, even impossible, to demonstrate its presence and to prove its etiologic significance The classification of food allergy is shown in Table 131

Psychosomatic factors may be important in activating and altering latent allergic symptoms To the chore of collecting data on the incidence of food allergy by history or by trial-and error methods may be added the difficulties of comparing the results of skin testing by different investigators, using food extracts of varying potencies, and employing varying skills and methods of testing Even when standardized extracts and techniques of skin testing are a constant as with a single investigator, the results may be unsatisfactory, since approximately one-half of the authentic food allergic cases fail to give positive skin tests

The majority of cases of food sensitiveness occur in early life From a study of 200 cases of bronchial asthma,[73] it was found by intracutaneous and clinical testing that only individuals of three years or younger developed symptoms from foods alone Inhalant substances, such as pollens, dusts, and animal danders, gradually replace the food allergies, so that by the age of ten to twelve years the majority of patients were no longer clinically food-sensitive although the skin test reaction often persisted In only 5 per cent of adult asthmatic patients could a food allergy be demonstrated as the sole excitant

It is generally agreed that the incidence of food allergy depends greatly on age In the infant sensitization to various foods is relatively high and ranks in importance with infection, while after the age of five years there is a tendency towards spontaneous disappearance of food allergy Therefore according to Chobot [3] the incidence of clinical food allergy is low in relation to that caused by inhalant substances and infection On the other hand Rinkel[74] feels that there is a higher incidence of food allergy in adults than in children although it is less readily demonstrable The comparative simplicity of the diet in childhood makes the diagnosis and food sensitivity easier then, furthermore, skin tests with food extracts are more reliable in children than in adults

FOOD ALLERGY IN CHILDREN

It is not known why some infants develop a specific sensitization shortly after birth although heredity may play a dominant role Spain and Cooke[18] have shown that where both parents are allergic, as indicated by the occurrence of bronchial asthma and/or hayfever, approximately 70 per cent

of the offspring will develop a clinical allergic condition by the age of ten years Where there is an antecedent unilateral history of bronchial asthma and/or hayfever, 50 per cent of the offspring will develop clinical allergic symptoms by the age of thirty years It would seem, therefore that both incidence and age of onset of clinical allergic conditions are influenced by the strength of the inherited trait Infections focal or constitutional and changes in the general health of the patient may play an important part in predisposing to the development or precipitation of allergic manifestations

It is significant that Rowe and Rowe [5] and Stoesser [6] found allergy to food most important in asthma of early childhood while inhalants were more significant in the latter part of the preschool period It is of interest that Ratner and Untracht [7] found that 5 per cent of 500 allergic children were sensitive, clinically and by skin test, to a single food—egg In the child as in the adult, the allergic process can affect any of the body systems

Types of Sensitizing Foods—Milk and egg are usually the first foods to which the infant becomes sensitive probably because they are among the initial foods comprising his diet In Clein s series of 140 allergic infants,[23] 1 out of every 15 was sensitive to cow's milk Among the conditions they developed were eczema, pylorospasm and colic, while some felt "unhappy all the time" Less common symptoms were cough, choking and gasping nose colds, constipation, asthma anorexia attacks of sneezing and toxemia

Direct skin testing by either the scratch or intradermal methods is rarely employed in such cases because of the threat of a possible violent reaction to the use of an excitant of high potency The diagnosis is usually established by the history the indirect skin test method, the food diary, and trial and-error procedures

Sensitization to milk is frequent and presents a considerable though essential replacement problem In the case of other foods simple removal is sufficient but where milk is to be avoided, some substitute that fulfills the nutritional and mineral requirements must be given to the infant and young child Such proprietary products as Mullsoy Soybean or S M A are often satisfactory milk substitutes, unless the infant be sensitive to soybean (a chief constituent of these preparations [9]) in which case Nutramigen may be tried Specifications for their use are supplied by the makers of all these substances Goat's milk, fresh or canned often offers a highly satisfactory replacement, although an allergenic factor common to both cow s and goat s milk may prevent its use

The infant or child highly allergic to egg must avoid all traces of it, and poultry as well In those with a more moderate degree of sensitization, the white of egg may be the excitant the yolk being readily tolerated as well as poultry Fortunately most infants and children do not demonstrate an exquisite degree of food intolerance and can satisfactorily follow a diet which need not be too restricted provided heat-treated or cooked items are used Ratner[30] has offered such a diet which has proven very helpful

Hypo allergenic Heat Denatured Diet for Children [30]—This diet is deficient in ascorbic acid, therefore 100 mg of ascorbic acid must be added daily

As the child grows older, the phase of physiologic maturity is reached

and the earlier sensitizations spontaneously disappear in the majority of cases. While many investigators emphatically disagree, Rowe,[31] and Rinkel[4] consider that the cereal grains are the most common food allergens, corn and wheat being the most frequent causes of chronic food allergy. Other food allergens of importance to the allergic child, as well as to the adult, are meats, especially beef and pork, poultry, seafood, fruits, vegetables, nuts, seeds, and chocolate. Treatment consists in removing the offending food from the diet. This will be discussed subsequently.

FOODS ALLOWED

1. Milk. *Only* evaporated milk or Mullsoy. Dextrimaltose may be added q.s.
2. Eggs. *Only* 30 minute hard *boiled* eggs.
3. Cereals. All cooked and prepared cereals (Pabulum, Pablena, oatmeal, rice, Farina, barley). All manufactured cereals such as corn flakes, Puffed Rice, etc. Cereal foods such as spaghetti, macaroni, noodle.
4. Breadstuffs. *Only* Melba toast, *Triscuits, Rye Krisp, Zwieback (must be baked again).*
5. Soups. All *clear* soups and all other soups whose ingredients are thoroughly cooked. (Do not add seasoning, bread, crackers, parsley, cheese egg drop, after the soup has been cooked.)
6. Meat and Poultry. Boiled or stewed only—beef, lamb, veal, chicken, turkey, ham, pork.
7. Vegetables. All vegetables thoroughly boiled.
8. Fruits. All cooked or stewed fruits, grape juice, cranberry juice.
9. Desserts. Gelatin, stewed fruits, puddings without egg and made with evaporated milk *only*.
10. Beverages. All bottled soft drinks.
11. Miscellaneous. Hard candies, jelly, marmalades.

NOTE. For eczema cases, include in the diet Mullsoy, corn oils (Wesson, Mazola), lard, bacon, wheat germ oil, for their unsaturated fatty acid content.

Malnutrition and Allergic Conditions.—Cannon[3] has emphasized the fact that intracellular globulin, including antibody globulin, acts as a protein reserve which can be called upon to replenish plasma proteins and with which these tend to remain in equilibrium. Low protein diets, or any interference with the rebuilding of protein reserves, leads to hypoproteinemia and progressive exhaustion of antibody reserves. This is true in conditions with severe tissue protein depletion, such as starvation, sprue, intestinal tuberculosis, and ulcerative colitis. Such exhaustion of antibody reserves explains the increased susceptibility to infection.[32] Kolmer[33] suggests that the peculiar increased tendency to infection in some cases of diabetes mellitus may be due to deficiency in the synthesis of antibody globulin by the cells of the reticulo-endothelial system. The diabetic is less able to form antibody than the normal individual due to an increased glyconeogenesis and, as a consequence, a large protein deficit may occur.[34–36] Wohl *et al.* have recently shown that low antibody response to antigenic stimulation in diabetics appears to bear a relationship to blood

protein levels rather than to fasting blood sugar levels, furthermore, oral supplementation with casein concentrate or lactalbumin hydrolysate enhanced antibody formation [37]

While most of the studies on the effect of malnutrition on antibody formation have concerned immune types of antibody, this same mechanism would also be apt to influence the skin-sensitizing antibody of the allergic individual The diminution or temporary disappearance of allergic symptoms such as urticaria, dermatitis, headache, and bronchial asthma, reported in individuals suffering from wartime malnutrition might conceivably be explained on this basis Not only is the degree of exposure to the specific protein probably decreased but there may be a deficiency in the reserves of antibody globulin necessary for the reaction with antigen to produce allergic symptoms The temporary lessening or loss of sensitization effects during acute illness however, cannot be explained upon this basis Relief from allergic symptoms even those of intractable bronchial asthma[38] and allergic dermatitis,[39] occurs frequently during acute intercurrent infections, such as lobar pneumonia [40] Kaposis' varicelliform eruption,[41] and measles [38] Such remissions would seem to be due to the mobilization of endocrine defense mechanisms during fever [4] an ACTH-like effect resulting from the release of steroid hormones [43]

Severe allergic conditions may have an adverse effect upon nutrition The individual with uncontrolled bronchial asthma is frequently undernourished, since he has come to realize that the lightest of meals may cause embarrassed digestion and abdominal distention with a consequent heightening of the asthmatic distress Anorexia nausea flatus diarrhea and constipation may result from apprehension concerning his health and from nervous tension caused by fear of precipitating an attack by the unwitting ingestion of some highly potent excitant, unidentifiable in some food preparation Anemia, avitaminosis underweight and, in the child lack of proper growth, with a reduced vital capacity are the evidences of impaired nutrition The interruption of sleep, respiratory or intestinal symptoms, or irritability and tension due to antiasthmatic stimulating drugs such as ephedrine may intensify the problem One of the first evidences of an improved allergic status is a gain in weight

In forms of severe food allergy, such as urticaria dermatitis, gastroenteritis colitis, and headaches, evidences of malnutrition often result from self inflicted, but usually unjustified curtailment of the diet The whims, fads, and phobias regarding food allergy which plague many persons both allergic and non allergic, force upon the physician the added responsibility of attempting to re-educate the patient, to reassure him and to encourage him to adopt an adequate diet

Food Allergy — *Diagnostic Methods* — *History Taking* —The presence of a food allergy is often simple to identify in the immediate type, but frequently difficult to locate in the delayed type It may be established by (1) the history, (2) cutaneous tests (3) food diary and (4) clinical tests employing trial-and error methods and restrictive diets History taking is the most important of all diagnostic procedures, and should be completed first It may provide information of great consequence not only as to the specific food causes, but also as to the degree to which they affect the

patient. With such knowledge, the investigator is forewarned, and may avert what might have been a hazardous exposure of the hypersensitive patient to the active food excitant by routine skin testing or clinical trial. In the immediate reaction type, where symptoms follow so swiftly upon exposure to the exciting food, the patient is usually fully aware of at least the more obvious and more potent food factors and the extent of disturbance they produce. The individual who describes the prompt development of edema of the lips and tongue upon accidental contact with traces of egg, nut, or fish, or who reports asthma from the inhalation of their odors, is not a candidate for further exposure to such foods by skin test or by ingestion experiments. Until the history and the degree of sensitivity can be verified, testing should be scrupulously avoided with those food excitants described as producing swift, severe symptoms; this is especially the case when the route of contact is by surface exposure of mucosa or skin, *or by inhalation of food odors, such as those of fish, meat, celery,* banana, or onion. Cases with a history of such a high degree of sensitivity *should be investigated by the passive transfer method.*

A comprehensive investigation of the occurrence of allergic conditions in the patient and his family should be obtained, since the presence of bronchial asthma, allergic coryza, or hay fever in the antecedent or collateral members of the family furnishes evidence of the inherited nature of sensitivity[17, 18] and strongly suggests that cutaneous tests will be of value. An inherited capacity for vigorous allergic response is usually present in food-sensitive cases with an immediate reaction time. Sensitivity in any form may show itself in other members of the family, and at times the same specific food cause and the same pattern of symptoms may persist through many generations. In La Roche's case[44] members in 4 generations of a family developed acute gastrointestinal symptoms from the ingestion of eggs, and Spain[65] had a case where gastrointestinal allergy to milk was present in 3 successive generations.

A point of diagnostic importance is the character of the symptoms. They may be acute, explosive in nature, and even hazardous to life in the immediate reaction type, insidious and obscure, although severe, in the delayed reaction type. A description should be obtained of the frequency, intensity, and duration of the symptoms, their paroxysmal or continuous character, their relation to meals, and to the daily, weekly, or monthly routine of the patient. Such correlations may usually be established through the maintenance of a food diary. Usually, the more acute the attack, the more brief the reaction time. The length of the symptom free periods between attacks depends upon the frequency of exposure to the food excitant. The attacks may be of a cumulative nature, as when a food eaten regularly, usually daily, becomes irritating only when the limit of tolerance is reached.

A characteristic of food allergy of the immediate reaction type is the fact that symptoms of overwhelming intensity may result from exposure to minute amounts of the food factor; here the symptoms speedily reach a crucial stage marked by almost instantaneous nausea, vomiting, diarrhea and asthma, and by ominous attacks of urticaria and angio edema. Individuals subject to attacks of such great intensity live in a continual state

of dread and apprehension, due to the threat of sudden diarrhea or of edema which may swiftly involve an area of such vital importance as the tongue or larynx Such persons are usually quite aware of the inciting food cause such as egg, nut, or a seed, but may be unable to avoid it completely, due to its presence in sauces, salads, or in a multiplicity of commercially prepared food mixtures An exquisite degree of sensitiveness to egg has forced one patient to avoid all food and drink outside the home and to use china and silverware kept constantly segregated from that employed in the household, for fear of contamination with egg in washings and handling Such patients, fortunately rare, may have multiple abdominal scars the results of repeated emergency operations necessitated by acute intestinal episodes, usually due to edema of the gut In their abruptness and severity, the symptoms successfully mimic those of the acute surgical abdomen resulting from such varied causes as volvulus intussusception mesenteric thrombosis, biliary colic, and acute appendicitis The surgeon even if he is aware that the symptoms may be due to a food allergy may be forced to operate in order to resolve the dilemma of whether food allergy or infection is the etiologic factor

Both severity and periodicity of symptoms of food allergy may be influenced by other associated and intimately linked allergic conditions Attacks of hay fever or bronchial asthma for instance may intensify the attacks of a food allergy or activate a latent food allergy It is a frequent observation that hay fever patients are able to ingest without allergic discomfort such foods as peaches, melon, sweet corn, chocolate or seafood except during the hay fever season when they are contending with intense and disturbing symptoms of pollenosis At these times, such food excitants may cause dermatitis, urticaria bronchial asthma or increased coryza The skin tests are often positive to the exciting foods not only during the pollen periods, but nonseasonally

In food allergy, as in other types of sensitivity and indeed in many other entirely different maladies, the frequency and severity of symptoms may be influenced by worry, anxiety and states of nervous tension In searching for a diagnosis, the physician must be fully aware of the complexities produced by such psychosomatic factors These are obviously operative in many individuals and may well prove an obstacle to improvement even where the physical factor the offending food is known A young housewife whose urticarial attacks were identified by positive skin test as due to celery was able to eat it without ill effect once the problems of her household budget were solved Occasional attacks occurred when celery was eaten at the first of the month, when the question of payment of bills was acute Considerable time, effort and patience must be expended by both physician and patient in collecting data on the dietary habits and reactions to food of the patient being studied No filling of blank history forms, no pattern of routine questioning is sufficient, since problems in food allergy differ so considerably among themselves Questioning and cross-questioning is essential especially in those cases with a delayed reaction time and negative skin test results [29] Such inquiry may offer the only clue to possible food factors Foods notorious for their outstanding antigenic activity and for their high incidence as excitants should be particularly

suspected These are, in most instances, ingested uncooked, hence with their characteristic proteins unaltered by heat They are milk, eggs, seafood, nuts, seeds, as mustard, chocolate, orange, tomato However, not only these but the individual items in all food groups, such as meats, sea food, fruits, vegetables, cereals, beverages, and spices, must be considered separately and in detail

Foods Eaten to Excess —Patients may eat immoderate amounts of a food because of food fads, efforts to gain or lose weight on unbalanced diets, or to economize Milk, egg, tomato juice, orange juice, and chocolate are common offenders A candidate for the football squad may drink several quarts of milk daily to gain weight, a dowager may consume excessive quantities of orange or tomato juice to lose weight, a stenographer may eat many chocolate bars to save lunch money Such extremes may lead to food intolerance, where a moderate and less monotonous intake of the same foods would cause no discomfort

Foods Eaten Though Disliked —Dislike of a food may be only a whim or a fancy, but it should be regarded as significant until proven otherwise Aversion to egg or milk in children may be the result of Nature's protective effort, often misinterpreted by parents

Foods Eaten, Though Causing Recognized Mild Related Allergic Symptoms —A patient may be fully aware that a food, such as chocolate, may cause stomatitis, without realizing that it also produces his allergic headaches Any food described as causing mild associated effects should be placed on the suspect list

Foods Eaten Though Known to Have Caused Earlier, Now Absent Forms of Sensitivity —A patient may remember that in childhood a severe chronic dermatitis disappeared when a food such as egg, was eliminated from the diet although its return to the diet in recent years, was not followed by a reappearance of the dermatitis It is not realized that the present allergic manifestation, such as colitis, may be the result of a less obvious sensitization to the same food

Foods Eaten Though Known to Cause Allergic Symptoms in Another Member of the Family —A familial allergy to a food such as egg or milk, in an antecedent or collateral member of the family, directs suspicion against this food as a cause of the patient's symptoms

Such prolonged investigative procedures, applied to all types of foods, may often prove pleasurable and exciting to the patient who delights in discussing his diet, but they may prove wearisome to the physician, they are certainly not adaptable to mass production methods Each patient is a separate and different problem, upon whom adequate information cannot be obtained in a few minutes or at a single visit Only after the expenditure of considerable time and effort can satisfactory data be obtained

The Immediate Reaction Type of Food Allergy —In this type, due to the brief interval between ingestion of the disturbing food and the occurrence of symptoms, the patient is able to inform the investigator at least partially of the exciting causes and of the degree to which they affect him He may, however, be unaware of the importance of related, but possibly less disturbing food substances, or that certain preparations may contain a food he knows to be an offender Thus an individual may be conscientiously avoiding egg as such, while continuing to eat food mixes containing egg

Upon skin test, definitely positive results are usually obtained with the extracts of those foods known to the patient for their immediate effect. As previously stated, such tests may be hazardous and should usually be avoided. Skin tests should be completed, however, with the extracts of other foods which may cause a definite but less obvious allergic disturbance.

Cutaneous Testing Procedures.—(*a*) *The Direct Method.*—Whether the scarification or the intradermal technique be employed, the diagnostic skin testing procedure should not be attempted until the history has been completed. A full discussion of the methods of cutaneous testing of foods is not pertinent to this chapter and may be readily found in many textbooks upon allergy. It should be mentioned, however, that frequently foods suspected and subsequently proven by clinical test to be authentic causes of immediate symptoms cannot be identified by skin test. Such negative effects are due in many instances to the disparity between the food as eaten (often altered by cooking) and the extract of it which is prepared from unheated material. Then, too, it may well be that many food extracts are rendered ineffective by changes resulting from the chemical manipulations essential to their preparation, and by changes occurring during storage. Also frequent are false positive reactions, due to nonspecific irritation of the cells of the skin. Despite these handicaps, cutaneous testing with food extracts is a useful and necessary procedure.

(*b*) *The Indirect Method.*—Direct testing of the skin may be contraindicated due to the young age of the patient (three years or less), the presence of eczematous or lichenified skin, or the threat of an extreme degree of sensitization. The sera from allergic persons of the immediately reacting type usually contain skin sensitizing antibodies responsible for the development of the wheal characteristic of the positive test.[4] Such antibodies may be shifted to the skin of a normal individual by intracutaneously injected deposits of the allergic serum, conferring temporary and local sensitization to the food excitants which are disturbing to the patient. This phenomenon can usually be shown by the positive results upon testing the serum sites with specifically offending antigens. This procedure has its limitations, but is relatively dependable and usually safe, although systemic reactions (vertigo, faintness, diarrhea, and oppression of the chest) have been known to occur in normal recipients in whom sites, made with serum from an exquisitely sensitive patient, were tested with extracts of excessive high potency.

The Specifically Restricted Diet.—Foods which give a positive reaction in direct or indirect skin tests (as indicated by an immediate wheal with pseudopods, itching, and a surrounding zone of erythema) should be retested for verification; if the reaction is again positive, they should be removed from the diet on the assumption that they are at least partially the cause of the patient's symptoms. He should be supplied with a written list not only of the foods banned but of those permitted. A typed or printed form may be adjusted to each person's needs by crossing from the list all culpable foods that are to be avoided.[46] In the adult suffering from chronic bronchial asthma or chronic allergic enteritis or colitis, it is also advisable to have the patient avoid all flatulence producing foods even though they are not incriminated as specific excitants (Table 132).

TABLE 132.—DIET LIST TO BE GIVEN ALLERGIC PATIENT

This diet is not to be continued indefinitely without supervision (Report for possible revision at the end of 4 weeks.)

Avoid those foods which have been crossed out. Use all other foods.

Dairy Products

Milk, cream, ice cream, sherbets, milk soups and other milk containing foods (see Milk-poor Diet below)
Butter, cheese, except cream cheese and cottage cheese
Egg, unless hard boiled for ten minutes, and egg containing foods, as griddle cakes, waffles, egg sauce, etc (see Egg-poor Diet below)

Meat and Fish

Chicken, duck, goose, turkey
Bacon, crisp, smoked ham
Fresh pork and pork sausage, lard
Lamb (roast, chops, kidneys)
Beef (roast, steak, calves liver, chipped beef), all beef products
Veal (roast, chops, kidneys)
Shellfish, except oyster
Fish (see Seafood-free Diet below)

Cereals or Breadstuffs

Wheat and wheat products, as macaroni, noodles, spaghetti, Cream of Wheat, Wheatena, Shredded Wheat, Bran Flakes, cookies, cakes, etc (see Wheat-poor Diet below)
Rye (pure rye bread, Rye Krisp)
Corn (cornmeal muffins, cornflakes, Farina, hominy)
Rice (also Rice Flakes, Cream of Rice cereal)
Oats, oatmeal
Barley
Soybean flour
Arrowroot
Tapioca

Vegetables

Artichokes	Eggplant	Pumpkin
Asparagus	Endive	Radish, horse radish
Beans, all types	Green pea	Spinach
Beets	Green pepper	Squash
Broccoli	Lentils	String benas
Brussels sprouts	Lettuce	Sweet corn
Cabbage, sauer kraut	Mushroom	Sweet potato
Carrots	Mustard	Tomato
Cauliflower	Okra	Turnip
Celery	Onion (baked or boiled)	Watercress
Chicory	Parsley	White potato (baked)
Cucumber	Parsnip	

Fruits

Apples	Grapefruit	Plums
Apricots	Grapes	Prunes
Avocado	Honeydew melon	Raisins
Banana	Lemon	Rhubarb
Berries	Lime	Strawberry
Cherries	Orange	Tangerine
Cranberries	Peaches	Watermelon
Cantaloupe	Pears	
Date	Pineapple	
Fig		

Beverages

All alcoholic drinks including beer ale wine
Chocolate cocoa
Coffee tea cola drinks

Miscellaneous

Nuts peanut butter (see Nut-poor Diet below)
Condiments highly spiced foods
Foods fried in vegetable oils such as cottonseed peanut and corn oils
Excessively sweet food
Intensely cold foods or drinks
Olives pure olive oil
Gelatin
Permitted foods should not be used constantly but whenever possible in rotation

Milk poor Diet

Avoid

Milk buttermilk cream as such and in prepared foods as ice cream sodas milk sherbet Bavarian cream mousse custards gravie cream sauces soups chowders
Prepared flour mixes for home cooking
Malted milk hot chocolate or cocoa prepared with milk
Cheese
Evaporated powdered condensed milk (bakery products as pies breads and cakes containing small amounts of cooked milk can often be tolerated)
Butter and oleomargarine can usually be permitted in modest amounts
Study the label on packaged foods for evidence of milk or milk products content

Egg poor Diet

Avoid

Eggs Fresh frozen powdered cooked in any form
Egg containing foods such as
- Soups broths made with egg
- Prepared flour mixes for home cooking
- Waffles doughnuts pretzels
- Pancakes griddle cakes pastries French toast
- Macaroons meringues frostings
- Cakes cookies unless known to be egg free
- Breads with glazed crust
- Foods breaded with egg mixture
- Sausages croquettes meat cake containing egg as binder
- Poultry especially chicken if fricasseed or in broth
- Salad dressings unless known to be egg free Hollandaise mayonnaise and egg sauces
- Ice cream and sherbets unless known to be egg free
- Custards cream candies fondants Bavarian cream
- Marshmallows
- Baking powder containing egg white
- Prepared drinks containing egg or egg powder for insomnia or underweight
- Study the labels on packaged foods for evidence of egg in any form
- Avoid virus vaccine made in egg as for influenza spotted fever yellow fever

Seafood free Diet

Avoid

Fish shellfish fresh canned smoked pickled fish liver oils and concentrates in vitamin preparations
Fish and shellfish stews bisques broths soups salad hors d oeuvres caviar
Avoid licking labels which may contain a fish glue adhesive
Avoid injections of fish origin in the treatment of varicose veins

TABLE 132.—DIET LIST TO BE GIVEN ALLERGIC PATIENT—(*Continued*)

Wheat poor Diet

Avoid

White whole wheat, cracked wheat flour in breads waffles, griddle cakes dough nuts muffins pastries pies, cakes crackers, spaghetti, macaroni, dumplings pretzels, zwieback, noodles
Corn bread, unless known to be wheat-free
Soy bread, unless known to be wheat-free
Rye bread unless known to be wheat free
Gluten bread
Breakfast cereals dry or cooked, containing wheat, whole wheat, cream soups Farina or bran
Custards, gravies, sauces containing wheat
Breaded foods prepared with wheat
Coffee substitutes containing wheat, beer, ale
Prepared meats, as sausages, frankfurters, meat loaf, croquettes made with wheat
Prepared mixes for biscuits muffins pastries pie crusts, cookies
Study the label on prepared foods for evidences of wheat or wheat product content

Nut poor Diet

Avoid

Nuts of all types also peanuts (although a member of the bean family) cottonseed meal in health and laxative breads soybean bread
Nut crumbs on cookies cake icings, ice cream
Candies containing nuts
Salad oils, lard substitutes margarines made of cocoanut, soybean, cottonseed or peanut oils (many are so made) (Olive oil permitted)

Individuals highly sensitive to nuts are often allergic to seeds such as cottonseed flaxseed, mustard (by external application in poultices as well as when ingested as foods) beans peas Legumes such as peas beans lentils are often allergenic factors in the patient sensitive to nuts but some patients tolerate legumes, such as peanuts despite high degrees of nut sensitivity

Patients sensitive to milk egg, wheat, or nuts, must be cautioned against the use of many of the preparations and food mixes supplied by manufacturers Such processed substances may contain the specific food excitants in quantities sufficient to produce allergic symptoms, as in the case of egg and milk in pancake mixes for home use Since the labels on packages of such products list all the ingredients, the patient should be urged to develop the habit of reading all such labels as a protective measure Fish sensitive patients must be warned against acquiring the habit of licking labels While adhesives used on postage stamps and many envelopes are not of fish origin fish collagen is used as the adhesive upon some types of labels, stamps, and stickers

In the diet prepared for the patient, rigid restrictions against more than one or two food items are rarely permanent Early changes are often desirable in an effort to enlarge and simplify the diet Once the patient becomes symptom-free, the banned foods are tried singly, at three-day intervals, in a trial-and error procedure, as outlined subsequently The problem of maintaining proper nutrition is simplified by providing the patient with an inexpensive pamphlet, "Food Charts,"* which furnishes

* American Medical Association 535 North Dearborn Street Chicago 10 Illinois

data upon the mineral and vitamin content of important foods Where added vitamin preparations are indicated the synthetic varieties should be employed if possible

The Delayed Reaction Type of Food Allergy —In those cases where the interval is prolonged, four to seventy-two hours elapsing between contact with the food and appearance of symptoms, not only is the cause usually unknown to the patient, but the allergic nature of the problem often is unknown, as well Unfortunately in just these instances, where the skin testing procedure would be most helpful, it fails In at least some instances the negative results upon test are due to a lack of the proper antigen, which may not be the food itself but some digestive product requiring several hours for its appearance and its allergic effect upon the patient This was true in Cooke's[47] case where allergic symptoms appeared several hours after the ingestion of milk Skin tests were negative to milk itself but positive to the milk proteoses Where neither history nor skin test affords information, but where there is reason to suspect an active food allergy, paroxysmal or continuous, an attempt at diagnosis should be made by food diary maintenance, dietary elimination and trial and error methods

Food Diary —Entries should be made by the patient each day of the separate items of food beverage and drugs ingested at each meal between each meal, and at bedtime At the end of the day's entry the patient should note any occurrence or continuance of his allergic symptoms Once weekly the physician should attempt to correlate repetitive symptoms with repetitive ingested items, the interval of from four hours to three days being a constant for each suspected item Should it be found for instance that headache occurred consistently on the third day following the ingestion of egg, that food should be suspected but if the interval proved to vary, being twenty-four hours at some entries and three days at others, the case against egg would be weakened, as too it would be if headache did not occur in the majority of instances after egg was ingested Foods suspected should be banned until subsequent verification of their allergenic importance can be attempted by trial-and-error procedure

Simple Elimination Diets —The simplest attempt at elimination consists of removal from the diet of those foods most notorious as excitants milk, egg (but not at the same time as milk) seafood nuts seeds chocolate orange, tomato Care must be taken to explain to the patient the need for thorough avoidance, and he should be provided with a list of foods or food compounds in which the banned items may be present in disguised form, as shown in Table 132 in the Milk-poor, Egg poor Seafood poor Wheat-poor, and Nut poor Diets Few patients object to abstinence from these food items for a four-week period—usually sufficient for a proper evaluation Occasionally the chronic nature of the symptoms requires a longer period for evaluation If promising results have been obtained from the restricted diet the patient becoming symptom-free the diet should be continued and at intervals of thirty-one days, the several banned items should be tried separately, those showing negative results, usually the majority, should be returned to the diet

Trial-and-error Procedure —If the patient is so fortunate as to become symptom-free as a result either of this relatively simple dietary procedure, or of restrictions based on positive findings in the clinical history or skin test, an attempt should be made to verify the fact that the excluded foods were offenders Each banned item, obtained from the original source and prepared as identically as possible, should be separately and cautiously introduced into the diet by feeding a small portion on an empty stomach, preferably one hour before the midday meal It is helpful in eliminating the personal equation if the food can be given in a disguised form, so that the patient is unaware of its identity, however, this is often impossible If no symptoms are induced, the food is tried again after an interval of three days, *in double quantity* *If no symptoms occur from the first and second* attempt, it may be concluded that the food under study may be eaten without discomfort, at least in moderate amounts and infrequently, although it must be remembered that a cumulative effect is always possible If symptoms appear, the suspected food is eliminated, to be tried again once the patient is symptom-free The same or even a lesser amount of the food is to be eaten, depending upon the severity of the condition previously produced The eliciting of symptoms typical of the patient's allergic complaint upon both first and second trials is presumptive evidence of a positive food cause if the patient was aware of the item under study, it may be considered positive proof if the food was fed in a disguised form If either the first or second test alone be positive, further study is necessary

The Rigidly Restricted Diet —Where this relatively simple procedure is not successful, more austere methods may be necessary The rigidly restricted diet is justified only in patients with severe, presumably allergic problems, such as recurrent headaches, urticaria, edema or colitis, and should not be employed in children, or in the severely ill (Table 133) The

TABLE 133 —THE RIGIDLY RESTRICTED DIET

Days 1–3	*Day 4*	*Day 5*	*Day 6*
Boiled rice	Add	Add	Add
Weak tea	Carrots	Lamb (chops roast stew)	Grapefruit
Lemon slices	Beets		Prunes
Cane sugar	Lettuce		Pears
Butter	*Gelatin (plain)*		
Salt			

No other foods than those specified are permitted There is no limit in quantity to any of the items The gelatin may be flavored with lemon and sugar Report to the office on the seventh day Record weight at the beginning of the diet and each seven days

In its restricted form this diet is temporary Food items are added each second day beyond the seventh day until the diet is well rounded Withhold all vitamin and *mineral products for the first three days then employ those which are made synthetically* and therefore are usually nonallergic

choice of foods is limited to the specific items but the quantities ingested are not curtailed With symptoms occurring frequently, at daily or weekly intervals, the patient's preferences may be consulted in the selection, after

the first day, of the three vegetables, the meat and the three fruits to be studied Beef or chicken may thus be substituted for lamb and other vegetables and fruits for those listed for the first five days of the diet If improvement in symptoms has occurred at the end of the week, additional food items may be attempted singly and at intervals of three days, by trial and error procedures, until the daily menu meets the nutritional requirements of the normal diet If at the end of two weeks no improvement has occurred, the diet should be replaced with a similar one with entirely different food constituents If this should prove unsuccessful, the presence of a food allergy is doubtful

Where the symptoms ordinarily occur at intervals of seven to fourteen days or longer, symptom-free periods of two to four weeks are usually required to determine whether offending foods have been removed from the diet In such instances, the elimination procedures of Rowe are most useful, having the advantage of offering specific dietary measures, pertinent menus[31] and recipes[48] as well To the urban dweller, dependent upon restaurants for his meals, the use of these and all other types of restrictive diets poses a formidable problem

Other Diagnostic Measures —No change in tissue function or tissue construction temporary or permanent is pathognomonic of food allergy Food allergy is protean in its clinical manifestations and may mimic many other physical ailments due to entirely different causes Even in gastrointestinal allergy of food origin where ingestion of a specifically exciting food produces sharp pathologic changes, demonstrable by *x*-ray such as edema of the mucous membrane, gastric retention and hypermobility with segmentation of the small intestine,[49–51] the effects are not diagnostic of allergy as pointed out by Cooke [2]

There are no laboratory procedures of specific diagnostic importance Even the demonstration of an eosinophilia may only suggest the presence of an allergic condition

The Nonspecific Diet in Chronic Bronchial Asthma —The chronic adult sufferer from bronchial asthma usually of infective origin is frequently distressed by anorexia, nausea abdominal distention, gaseous eructations and constipation These disturbances he erroneously attributes to the presence of a food allergy, since the distress appears soon after a meal, and intensifies his asthmatic breathing by upward displacement of the diaphragm with resulting diminution of the vital capacity Such intestinal manifestations, together with constipation, are due to lowered gastrointestinal tone and are probably caused by anoxemia of the mucosa and muscularis [5, 53] as they are in congestive heart failure Since the chronic asthmatic patient frequently suffers from an associated or secondary myocardial dysfunction the avoidance of all flatus producing foods is of the utmost importance Legumes of all types, especially dried the cab bage family turnip sweet potato, melon chocolate cheese shellfood, nuts and highly spiced, fried or greasy foods, including salad oils are especially disturbing as are carbonated beverages, beer and ale (Table 134)

The nonspecific diet is often applicable to adult cases with allergic intestinal conditions In this diet the restricted items are those which cause abdominal distention The list of foods is quite similar to that prepared

by Borborka[54] and mentioned by Bromer and Stroud[55] in their discussion of the dietary management of congestive heart failure If there be any proven food excitant, it is of course also removed from the diet Changes may be necessary in deference to any associated systemic disease such as nephritis, colitis, gastro-enteritis, obesity, and rarely diabetes, these conditions require restrictive diets of their own which usually should take precedence over the nonspecific diet here submitted, unless the two can be blended

TABLE 134 —NONSPECIFIC DIET IN CHRONIC BRONCHIAL ASTHMA

AVOID

Milk, unless fat-free, cream ice cream
Cheese, except cream cheese and cottage cheese
Shellfish

Vegetables	*Vegetables (con't)*	*Fruits*
Beans all types except string beans	Green pepper	Apples raw
Broccoli	Lentils	Avacado pear
Brussels sprouts	Mustard	Cantaloupe
Cabbage	Onion	Honeydew melon
Cauliflower	Parsley	Raisins
Celery	Radish, horse radish	Strawberry
Cucumber	Sweet potato	Watermelon
Green pea	White potato	
	Turnip	

Miscellaneous

Nuts peanut butter
Coffee unless freshly brewed by Silex or other single filtration methods and not boiled or reheated
Tea unless not boiled
Chocolate cocoa
Beer ale
Carbonated drinks as cola drinks, ginger ale, etc
Condiments highly spiced foods
Oleomargarines salad oils as French dressing or mayonnaise prepared from vegetable oils
Foods fried in vegetable oils such as cottonseed, soy, peanut and corn oils
Excessively sweet or salty foods
Intensely cold foods or drinks

The asthmatic patient should eat lightly, in moderation, with between meal supplements of fruit juices, tea, or milk, preferably fat-free No food should be taken after 6 P M , and he should abstain from any but the lightest foods during periods of mental stress, or acute asthmatic attacks He should eat slowly, deliberately, and, since his ability to assimilate his food is greater in the mornings, he should make his breakfast and his lunch the chief meals of the day A thirty-minute rest period after each meal is helpful

Alcohol in moderate amounts is apparently helpful to the chronic allergic patient since, when taken before meals, it stimulates the appetite, eases tension, and, by the liberation of histamine stimulates gastric secretion[56] It is helpful in relieving the asthmatic attack and, before the ad-

vent of epinephrine and antiasthmatic drugs was habitually employed especially taken hot, to control asthma[57]—a procedure which readily leads to its excessive use Its ability to increase the permeability of the gastro-intestinal mucosa may intensify the symptoms of food allergy, as is frequently observed when it is taken before a meal and its influence in dilating the peripheral vascular system[58] may be the cause of temporarily increased nasal obstruction, coryza, and sneezing in the case of allergic coryza due to foods or to inhalants

The Diet Indicated in Allergic Conditions —No rigid dietary measures can be established for the treatment of allergic disease, since its causes are multiple and its various manifestations may involve any of the major systems of the body If the allergic disease is of nonfood origin no specific diet is necessary, unless one is required for an associated systemic disorder If the allergic disease is the result of food sensitization the diet should be one from which the foods identified as important causative factors have been banned The nutritional requirements are the same as those of the normal non allergic person Far from being routine the diet prescription for an allergic patient must be specific individually modified and adjusted as the provocative food causes discovered may indicate

THERAPY IN FOOD ALLERGY

Specific Measures – The complete and prolonged elimination from the diet of the identified incriminating food or foods constitutes the specific therapy in cases of food allergy Immunization procedures with the food itself or its extract orally or parenterally administered are rarely successful and they are often dangerous especially in the highly allergic individual There should be proper substitution of other foods and the addition of necessary vitamins to maintain nutrition and to avoid monotony in the daily diet Where food allergy is suspected and the cause has not been determined by history or skin tests extensive trials with restricted diets intentional feeding diets (trial and error procedure) and other established diets as previously outlined should be tried

General Therapeutic Measures —The medications of value in the control of symptoms due to food allergy are the same as those used for similar symptoms in other allergic manifestations, regardless of cause It is beyond the scope of this chapter to discuss in detail these medications and their use Since, however dietary measures must almost always be accompanied by some form of therapy, the most important agents will be mentioned

(a) *Therapeutic Agents Useful in Acute Allergic Food Accidents* —Although comparatively rare, unexpected allergic emergencies due to foods may sometimes involve even the most wary and experienced of patients who are continually on their guard against chance contact with their specific food excitants Swift, devastating and extremely grave symptoms may result from a trace of egg in a food mustard in salad sauce or condiment nut crumbs in pastry, ice cream or candy or from accidental inhalation of the odor of a food such as fish banana, nut or celery Before he realizes its nature the fish sensitive patient may receive parenterally a

sclerosing agent of fish origin, or the egg-sensitive patient an egg containing virus vaccine against influenza, Rocky Mountain spotted fever, typhus, or yellow fever, or the pork- or beef sensitive patient may receive a highly disturbing injection of insulin or adrenocorticotropin (ACTH) or of liver extracts prepared from organs of the animal to whose proteins he is sensitive Allergic reactions have been reported following the drinking of milk from cows who were given slow absorption penicillin because of mastitis McLean[66] suggest therefore, that the food and drug law be amended so that dairy cows producing milk are never given slow absorption penicillin and that milk should not be sold to the public from sick cows receiving penicillin or other antibiotics for at least six days from the last dose Allergic reactions due to penicillin are appearing in increasing numbers and similar reactions following the administration of poliomyelitis vaccine which contains a small quantity of penicillin have occurred in extremely sensitive people[67] While this is not directly a food problem, Rinkel[68] claims that it is closely related to certain foods, namely those containing yeast He states that there is a synergism between various yeast containing foods and a penicillin sensitization, which in some instances at least is the cause of long continued penicillin urticaria (due to cross sensitization among the molds) Therefore, penicillin sensitive individuals should eliminate all foods containing yeast, including all fermented drinks, root beer, all cheeses, bread, vinegar and any of the cereal grain foods enriched with these products There is now available an enzyme, penicillinase (Neutrapen) which neutralizes the penicillin itself It catalyzes the hydrolysis of penicillin to penicilloic acid, which is nonallergenic The inhibitory action has been shown to be effective an hour after the injection of Neutrapen and to continue for four to seven days[69,70] As soon as signs and symptoms of penicillin reactions appear 800,000 units of Neutrapen should be injected intramuscularly If necessary the dosage may be repeated at three to four day intervals In anaphylactic shock Neutrapen should be given intravenously, followed immediately by an intramuscular injection plus supportive measures Recently Hyman[83] and Reisch[84] have reported severe reactions following the injection of penicillinase (Neutrapen) for penicillin reactions

Ill advised intravenous or clinical testing of the exquisitely sensitive allergic patient with his specific food excitant may swiftly cause overwhelming, even fatal effects, these may involve the respiratory, cutaneous and intestinal systems, as manifested in coryza bronchial asthma, cyanosis, massive urticaria, edema of the lips, tongue, larynx and skin, and various gastro intestinal symptoms In such accidents, time is of the essence Epinephrine 1 to 1000, 1 to 2 ml, subcutaneously or intravenously, should be given and oxygen administered if available Emergency hospitalization and tracheotomy may be required if there is edema of the larynx and asphyxia is threatened[71] Ephedrine and antihistaminic drugs are ineffectual in such situations, and the steroid hormones are often too slow in their action requiring a few hours to a day or two before their effect is produced However, intravenous therapy with 50 mg prednisolone or 100 mg hydrocortisone hemisuccinate in 2 ml of sterile water might act rapidly enough to meet the emergency Antihistamines, repository epinephrine and ephedrine should sustain control once the critical stage has

passed.[7] Morphine in 16.0 mg. (¼ grain) hypodermic doses may be used to control pain due to intestinal or uterine spasm, provided the possibility of an acute surgical abdomen can be excluded.

(b) *Therapeutic Agents Useful in the Common Forms of Food Allergy.*—The antihistaminic preparations in doses recommended by their makers are especially helpful in relieving pruritus and edema of food origin whether the distress be in the respiratory, alimentary or cutaneous systems. Food-provoked allergic rhinitis,[73] allergic bronchitis and even bronchial asthma (except the severe type) respond swiftly to the oral administration of antihistaminic preparations. Nausea, abdominal distention, diarrhea and acute distress of the intestine and colon due to food allergy may often be satisfactorily controlled by these agents, as well as the pruritus and congestion of allergic dermatitis, urticaria and angioedema. Many food-sensitive patients, fearful of attending dinner parties or banquets, where their exciting agents may be served in hidden or masked forms, are reassured by the presence in purse or pocket of an antihistaminic drug.

In some instances the administration of antihistamines have been followed by numerous side reactions. All preparations are capable of producing some degree of somnolence in some persons. Additional side reactions vary with the individual and with the dose and include drowsiness, vomiting, dryness of the mouth, constipation, confusion, urinary frequency, excitability and loss of judgment. Various cutaneous manifestations have also been reported. Isolated cases of respiratory distress and more serious blood dyscrasias have been described.[74] The topical use of the antihistaminic drugs[59, 60] and of local anesthetics for the erythema and pruritus of allergic skin disorders should be avoided, since it has been shown that sensitization to them may be induced by their repeated application in a cream or ointment base to the skin, especially if it be inflamed or fissured.

Epinephrine 1 to 1000, 0.3 to 1.0 ml. by subcutaneous injection, is useful in controlling the immediate and severe symptoms which follow the ingestion of a specific food excitant, whether they be those of coryza, bronchial asthma, urticaria, angioedema or gastro-enteritis. Where the symptoms are stubborn or protracted, epinephrine 1 to 500, 0.5 to 1 ml., by subcutaneous injection in a slowly absorbed vehicle such as oil or gelatin[75] is helpful; the latter vehicle is preferable where a nut or seed sensitiveness is suspected. Epinephrine 1 to 100 by nebulization may offer relief in acute cases.

Ephedrine sulfate, 8 mg. (⅛ gr.) in children or 25 mg. (⅜ gr.) in the adult, administered orally each two to six hours, is useful in respiratory distress. It is of little value in controlling allergic symptoms of the gastro-intestinal, cutaneous or other systems. The addition of phenobarbital in amounts equal to the ephedrine will often lessen the nervous tension produced by the latter drug.

Aminophyllin is useful in asthmatic attacks of food origin. It may be given orally each four to six hours, 0.05 gm. (¾ gr.) in the child, 0.1 gm. (1½ gr.) in the adult. Aminophyllin is also available in suppository form. In acute cases it may be given intravenously each eight to twenty-four hours, 0.1 gm. (1½ gr.) in the child, 0.25 gm. (3¾ gr.) in the adult.

Adrenocorticotropin (ACTH) by injection, 25 mg. each six hours for

twenty-four hours, then gradually reduced to 5 0 mg, may bring dramatic results in massive urticaria and angioedema Cortisone, given orally may be equally, though not as promptly, effective The initial daily dose of 200 to 300 mg, equally divided for administration each six hours, is gradually lessened, being discontinued within seven to ten days In chronic cases of urticaria or angioedema due to unidentified causes, maintenance doses of the steroids may be required for much longer periods Newer and better steroids have been developed during the past several years with the aim of increasing their potency, lessening the dosage and minimizing their side effects The currently available synthetic analogues of cortisone and hydrocortisone have as yet failed to demonstrate any physiologic effects not manifested by the parent fraction but the intensity of their biologic actions and the ratio of glucocorticoid to mineralocorticoid effects are altered Corticosteroid therapy is not a substitute for specific treatment of allergic conditions and should be administered as a supplement to immunologic management and other well established symptomatic measures The steroids should be reserved for acute allergic states such as intractable asthma, severe serum sickness, acute angioedema in the vicinity of the glottis and drug reactions Contraindications to the use of ACTH, corticotropins and the corticosteroids have been widely publicized They include hypertension, diabetes, pulmonary tuberculosis (active or inactive), peptic ulcer and psychic states Treatment with the steroids must be individualized and the well known precautions and complications incident to their use should receive close attention [76] The topical application of ACTH or corticosteroids for relief in allergic dermatitis should be used with caution, since sensitization to them may be induced [77 78]

Belladonna, atropine, and products with an atropine like effect, often combined with a barbiturate, are useful in controlling the abdominal distress resulting from the spastic intestinal muscle of allergic as well as of non-allergic origin Paregoric is helpful in controlling the diarrhea due to food allergy, while the use of secobarbital sodium (Seconal sodium), pentobarbital sodium (Nembutal), or sodium bromide, may permit a night's rest in the presence of an aggravating pruritus Topical applications of some phenol-containing preparation may allay the itching

Tranquilizing drugs are being used alone or in combination with steroid or other drug therapy for the relief of anxiety, tension and insomnia in patients suffering from allergic manifestations due to foods or other causes While these drugs are helpful in allaying some of the emotional problems of the allergic patient they must be administered with caution as side reactions have been reported following their use The reactions include nasal stuffiness, malaise, various forms of dermatitis, urticaria, angioedema, purpura, pruritis, laryngeal edema, jaundice, depression, cardiac arrythmias and blood dyscracias [79 80 81]

The use of aspirin to relieve pain should never be suggested to the allergic person until it is quite clear that is is well tolerated Severe, even lethal effects may be produced in the allergic by as little as 0 3 gm (5 gr) Aspirin is often present inconspicuously in the multitude of antipain and "anticold" medications and nostrums [82]

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Chapter 28

Nutrition in Rheumatism, Arthritis and Gout

By Theodore B Bayles

Introduction —"Collagen diseases," "group diseases," and "connective tissue diseases" are synonyms used to describe several diseases of unknown etiology They have certain similarities, similar sites of pathologic involvement, and barely possibly a common pathogenesis Clinically, the conditions involved are *rheumatic fever rheumatoid arthritis, periarteritis nodosa, lupus erythematosus disseminatus scleroderma, dermatomyositis* and perhaps malignant nephrosclerosis Rich[1] has suggested a common etiologic basis of tissue sensitization, but most observers agree that the similar pathologic findings may be explained by a similar response of connective tissue to a variety of insults Connective tissue has a limited spectrum of response to injury

In this poorly understood group of connective tissue diseases, nutrition has not been proved to be of *specific etiologic or therapeutic importance*, but debility, chronic disease state muscle wasting fever, gastrointestinal or kidney involvement (nephritis), poor appetite, etc make the matter of proper, adequate and full nutrition a problem of real moment to the patient and the clinician

Rheumatic Fever —The evidence strongly suggests that the immunologic insult of hemolytic streptococcus (Group A) infections to the susceptible human acts as the trigger in the onset of rheumatic fever The part played by dietary or metabolic factors in rendering the human susceptible has not been proved Once the rheumatic process has been established in the patient, there is no evidence that dietary factors can influence its course On the other hand common sense dictates attention to dietary intake For children[2] the following diet has been recommended—low in fat high in protein and carbohydrate, including 1 quart of skim milk, unlimited water, 5000 units vitamin A 400 units vitamin D, 100 mg vitamin C double the standard allowance of vitamin B complex and 15 mg of iron When rheumatic carditis and/or congestive heart failure is present sodium intake should be restricted to 1 to 2 gm daily

There is no positive evidence that a vitamin deficiency is a direct or indirect etiologic agent in rheumatic fever[3] A study of experimental scurvy[4] led to the conclusion that there was "only a superficial morphologic similarity between the articular lesions of scurvy and those of either rheumatoid arthritis or rheumatic fever" The importance of vitamin C in rheumatic fever has been lessened by the findings that ascorbic acid blood levels in rheumatic fever subjects and normals were the same on the same intakes[5] The unexplained observation by Massell[6] that large doses

of ascorbic acid (4 gm /day) apparently depressed *rheumatic activity* has not been confirmed or amplified

A great deal of investigation has attempted to relate the rheumatic process to hypersensitivity initiated by hemolytic streptococcus (Group A) infections, but even so Fischel concluded "there is, as yet, no clinical test for the detection of an allergic reaction in rheumatic individuals that does not occur in patients recovering from a streptococcal infection or certain other diseases" Certainly the effect of nutrition on this type of biologic reaction is far from clear at the present time

Studies on the social and hygienic factors in host susceptibility seem to incriminate crowding with consequent greater exposure to the hemolytic streptococci rather than the inadequate or substandard diets provided in substandard homes Nevertheless, Massell[8] states that clinical practice at the House of Good Samaritan, Boston, dictates a high protein diet with fresh fruit daily

Rheumatoid Arthritis —The patient's question, "What kind of diet do you recommend?" is too often incorrectly answered by the physician, either with a peremptory remark that it does not matter what the patient eats or, at the other extreme, by the imposition of a rigid program based on the physician's own dietary fetish No dietary deficiency has been causally related to rheumatoid arthritis, but we are dealing with a chronic, progressive, inflammatory tissue disorder in which good nutrition of the individual is of fundamental importance The victim of rheumatoid arthritis has a known negative nitrogen and calcium balance, muscle atrophy, decalcification of bone, and in the active state of the disease, decreased carbohydrate tolerance [9] We must point out that the active stage of the disease, with remissions and exacerbations, may go on for many years, and even a patient in apparent complete remission is subject to a relapse It has been said, "Once an arthritic, always an arthritic" With this lugubrious yet correct viewpoint, to disregard nutrition in this chronic disease is bad medical practice *The patient with rheumatoid arthritis has a systemic disease and is a sick individual*

Attempts to relate this disorder to specific dietary factors have not been successful Bayles, Richardson and Hall[10] found no evidence of significant dietary deficiency preceding onset of the disease Bauer[11] reviewed and discarded the various diets suggested in the past as not specific and perhaps harmful The decreased carbohydrate tolerance is probably related to the chronic inflammatory state rather than to a fundamental dyscrasia in sugar metabolism,[12] therefore, carbohydrate intake need not be decreased except to enhance protein ingestion The lowered serum albumin and elevated globulin may indicate hypersensitivity, chronic inflammation, or inanition

The diet* which we prescribe contains about 150 gm of carbohydrate, 80 to 100 gm of protein, 80 to 100 gm of fat, and 1 500 to 2 000 calories, depending upon the patient's relation to normal weight

* I acknowledge gratefully the preparation of the details of the diets in this chapter by Miss Madge I Myers, Director Department of Nutrition and Miss Jeannette M Albert Clinic Nutritionist, Peter Brent Brigham Hospital, Boston Mass

TOTAL FOOD FOR THE DAY

Amount	*Kind of food*	*Choose from*
4**	Milk exchanges	List I
Any amount	Vegetable exchange A	List II A
1	Vegetable exchange B	List II B
3	Fruit exchanges	List III
5	Bread exchanges	List IV
6–8	Meat exchanges	List V
0–4**	Fat exchanges	List VI

** Non fat milk will be substituted for whole milk or the fat exchanges will be eliminated from the diet depending upon the patient s relation to normal weight

MEAL PLAN

Breakfast	*Lunch*	*Supper or Dinner*
(1) Fruit exchange	(2) Meat exchanges	(3–4) Meat exchanges
(1–2) Meat exchanges	(1) Vegetable exchange A	(1) Vegetable exchange A
(1) Bread exchange	(2) Bread exchanges	(1) Vegetable exchange B
(1) Fat exchange	(1) Fat exchange	(1) Bread exchange
(1) Milk exchange	(1) Fruit exchange	(1) Fat exchange
	(1) Milk exchange	(1) Fruit exchange
		(1) Milk exchange

Bedtime

(1) Bread exchange
(1) Milk exchange
(1) Fat exchange

See page 693 for the explanation of the use of the method and the List of Exchanges

MEAL PLANNING WITH EXCHANGE LISTS*

The foods are divided into six groups called Exchange Lists Each food within a list has approximately the same food value and therefore, one food on a list can be exchanged with another food on the same list (See page 635)

Vitamins, over and above those furnished by a good diet, have not been proved to alter the course of rheumatoid arthritis, despite some evidence that absorption and utilization may sometimes be below normal in this chronic disease It has been established that vitamin A [13] vitamin B complex (thiamine hydrochloride, niacin riboflavin),[14] vitamin C,[15] E or K when studied directly, did not alter the symptoms or course of the disease

Administration of vitamin D in concentrated high dosage is potentially dangerous and of little or no value The toxic effects have consisted of polydipsia, polyuria, muscle weakness, headache, drowsiness, nausea vomiting and diarrhea—in decreasing frequency Hypercalcemia may cause metabolic calcification in soft tissues and more seriously in the kidney [16]

* Meal Planning with Exchange Lists published by the American Diabetes Association and the American Dietetic Association in cooperation with the Diabetes Branch Public Health Service Federal Security Agency

The anemia of rheumatoid arthritis is partially hemolytic in character,[11] t is not primarily due to iron deficiency, nor to inhibition by a "toxin" rom the disease of the normal hematopoietic process in the bone marrow lence once any concomitant iron deficiency has been corrected by oral dministration of iron, further oral iron will not improve the anemia Sin lair and Duthie obtained satisfactory rises in hemoglobin with intravenous ron in 38 of 51 cases, but 13 cases remained refractory Supportive blood ransfusions have only a transitory effect on the anemia of rheumatoid rthritis Cobalt therapy, in our experience,[19] has not corrected the nemia

In elderly patients with mild rheumatoid arthritis—and this disease ay often start in the sixth or seventh decade—supplementing the diet ith liver by mouth often has a salutary effect, but certainly this cannot e considered specific at the present time

Degenerative Joint Disease (Osteoarthritis, Hypertrophic Arthritis) — Degenerative joint disease or hypertrophic arthritis is more amenable to a utritional approach than rheumatiod arthritis Degenerative joint changes n weight-bearing joints, specifically the hip and knee, are the most serious linical and crippling problem in this disease While the joint damage may e secondary to a slipped femoral epiphysis poor posture, marked bowleg, r knock knee deformity, it is very often aggravated by obesity Obesity an be corrected by placing the patient on a subcaloric diet Weight loss lmost invariably alleviates the symptoms to a greater or lesser extent lowever, there is nothing intrinsic in the diet that produces the favorable ffect Most patients with degenerative joint disease lose weight more appily on a high protein moderately low fat, low carbohydrate diet, the mount of fat and carbohydrate will vary, but I try to give 80 to 100 gm f protein, 50 to 60 gm of fat, and 100 to 150 gm of carbohydrate

DIETS FOR DEGENERATIVE JOINT DISEASE (OSTEOARTHRITIS, HYPERTROPHIC ARTHRITIS)

A typical diet for an obese patient with degenerative joint disease of the nees or hips will contain approximately 100 to 150 gm of carbohydrate, 0 to 100 gm of protein, 50 to 60 gm of fat and 1,200 to 1,500 calories

TOTAL FOOD FOR THE DAY

Amount	*Kind of food*	*Choose from*
4	Milk exchanges (non fat)	List I
Any amount	Vegetable exchanges A	List IIA
1	Vegetable exchanges B	List IIB
3	Fruit exchanges	List III
2–4*	Bread exchanges	List IV
6–8	Meat exchanges	List V
3–4*	Fat exchanges	List VI

* The bread and fat exchanges will be adjusted depending upon the patient's relation to desired weight level

MEAL PLAN

Breakfast	*Lunch*	*Supper or Dinner*
(1) Fruit exchange	(2) Meat exchanges	(3–4) Meat exchanges
(1–2) Meat exchanges	(1) Vegetable exchange A	(1) Vegetable exchange A
(1) Bread exchange	(1–2) Bread exchanges	(1) Vegetable exchange B
(1) Fat exchange	(1) Fat exchange	(1) Fat exchange
(1) Milk exchange (non fat)	(1) Fruit exchange	(1) Fruit exchange
	(1) Milk exchange (non fat)	(1) Milk exchange (non fat)

Bedtime

(0–1) Bread exchange
(0–1) Fat exchange
(1) Milk exchange (non fat)

See page 636 for the explanation of the use of the method and the List of Exchanges

This dietary program has in my experience resulted in weight loss relatively satisfactory satiety, general well being an improvement in both weight bearing and non-weight bearing joints However, other factors, such as thyroid function menopausal hormone imbalance and the mechanical stresses and strains involved in degenerative joint disease make the evaluation of the effect of diet very difficult

Gout —Gout is a disorder of uric acid metabolism resulting in hyperuricemia—a high level of uric acid in the serum or plasma The normal serum uric acid varies from 2 to 5 mg per 100 cc of plasma or serum Patients with gout have levels of 6 to 10 and rarely up to 20 mg per 100 cc of serum or plasma In an unpredictable number of individuals with hyperuricemia, clinical gout or gouty arthritis will occur Hyperuricemia is transmitted by a single dominant autosomal gene which is not sex linked, only a portion of the heterozygotes for this factor develops gouty arthritis [1] Stecher Hersh and Solomon estimated penetrance of 84 per cent in the heterozygous male and 12 per cent or less in the female relatives Familial hyperuricemia is usually not present in males under the age of sixteen or in women until after the menopause The mechanism of hyperuricemia has been ascribed to (*a*) overproduction of uric acid in the body, or (*b*) diminished destruction of uric acid in the body or (*c*) decreased renal excretion of uric acid None of these theories has been conclusively proved Recently a variety of isotopically labeled compounds have been administered to birds, rats, and man When the isotope tracer is identified in various positions in excreted uric acid and in purines isolated from tissues it becomes apparent that the metabolic precursors of uric acid may be relatively simple compounds readily available from the 'metabolic pool [2,3-5] It seems likely that glycine is the nucleus about which carbon and nitrogen atoms become associated in the biosynthesis of uric acid [6]

This incontrovertible experimental evidence that simple available compounds in the body, such as carbon dioxide glycine, and ammonia may be synthesized into uric acid makes the dietary treatment of gout less vital than former authorities in this field thought Whether the above facts

preclude the possibility of dietary factors altering human uric acid metabolism is not as yet decided

A large fluid intake is helpful in eliminating uric acid, in preventing renal calculi and in retarding progressive involvement of the kidney Treatment of the azotemia associated with chronic gouty nephritis is similar to the treatment of azotemia due to other causes A high carbohydrate diet has a tendency to increase uric acid secretion, whereas a high fat diet tends to retard it and may in some patients precipitate gouty attacks Only those protein foods containing nucleo-proteins whose end-product in breakdown is uric acid need be considered A diet restricted to 100 mg of purine a day permits a 3-oz serving of meat, fish, seafood, peas, beans, or lentils a day Foods of high purine content should be excluded

PURINE CONTENT OF FOOD

A—High 150–800 mg /100 gm	*B—Medium* 50–150 mg /100 gm	*C—Low* 0–15 mg /100 gm
Not allowed	*One serving a day*	*Unlimited*
Sweetbreads	Meats	Vegetables (except as noted)
Anchovies	Fish	Fruit
Sardines	Seafoods	Milk
Liver	Peas	Cheese
Kidneys	Beans	Eggs
Meat extracts	Lentils	Cereals (except whole wheat)
	Asparagus	
	Cauliflower	
	Spinach	
	Mushrooms	

Of course, under no circumstance should the caloric intake of the diet be such as to increase the weight of a patient above his ideal There are many differences of opinion on details of this phase of therapy However, it would seem reasonable to expect that limitation of the intake of purines and promotion of the output of uric acid might have a beneficial effect over a period of years

The diet prescribed during the *acute* attack should be as follows

Breakfast	*Noon*	*Supper*
150 cc fruit juice	Cottage cheese salad	Cereal
150 cc milk	Toast and jam	150 cc milk
150 cc water	150 cc milk	150 cc water
2 eggs, boiled	150 cc water	Stewed fruit
	Stewed fruit	
1 pc toast with jam no butter	*4 P M*	
	150 cc water	*Evening*
10 A M	150 cc milk	150 cc milk or fruit juice
150 cc water	150 cc fruit juice	150 cc water
150 cc fruit juice		
150 cc milk		

DIET FOR INTERVAL GOUT

During the period between attacks the diet should be adjusted to the desired weight of the patient and, as pointed out, should not allow over-

weight A suggested diet for interval gout contains from 200 to 300 gm of carbohydrate, 75 to 85 gm of protein, 20 to 40 gm of fat, and 1,300 to 3 000 calories depending upon the patient s relation to normal weight (It should include 1 quart of skim milk and 2 quarts of water or sweet liquids Alcohol should be eliminated or taken sparingly and diluted, *i e*, highballs)

TOTAL FOOD FOR THE DAY

Amount	*Kind of food*	*Choose from*
4	Milk exchanges (non fat)	List I
Any amount*	Vegetable exchanges A	List IIA
1 *	Vegetable exchanges B	List IIB
3–6	Fruit exchanges	List III
4–6*	Bread exchanges	List IV
5–6*	Meat exchanges (3 only as meat)	List V
0	Fat exchanges	List VI
Any amount**	Sweet sugar jelly jam marmalade and dessert	

* See preceding list of foods to avoid
**If patient is not obese

MEAL PLAN

Breakfast	*Lunch*	*Supper or Dinner*
(1) Fruit exchange	(1–2) Meat exchanges	(3) Meat exchanges
(1) Meat exchange	(1) Vegetable exchange A	(1) Vegetable exchange A
(1–2) Bread exchanges	(1–2) Bread exchanges	(1) Vegetable exchange B
(1) Milk exchange (non fat)	(1) Fruit exchange	(0–1) Bread exchange
Jelly, jam or marmalade	(1) Milk exchange (non fat)	(1) Fruit exchange
Sugar (as desired)	Sugar (as desired)	(1) Milk exchange (non fat)
		Dessert (if desired)
		Sugar (as desired)

Between Meals	*Bedtime*
(1) Fruit exchange (if caloric intake is not restricted)	(0–1) Bread exchange
	(1) Milk exchange (non fat)

See page 636 for the explanation of the use of the method and the List of Exchanges

The methylxanthines (caffeine, theophylline, and theobromine) of coffee, tea, and cocoa are metabolized to methyl urates and are not deposited in the gouty tophus,[27] therefore these common beverages need not be avoided

In this chapter an evaluation of general medical treatment is not made, but it should be mentioned that Benemid a new uricosuric agent is perhaps the first significant advance in the treatment of gout since colchicine was introduced to clinical medicine three hundred or more years ago Benemid is a non toxic, continually active tubular reabsorption blocking agent which lowers, and keeps low, the large miscible pool and stored uric acid and urates in the body of gouty subjects

Miscellaneous —*Infectious arthritis* as classified by the American Rheumatism Association, refers to the specific infections of joints by known

bacteria, spirochetes, viruses, filterable agents, etc For dietary problem of infectious disease see page 555

Scurvy —We will consider this problem only insofar as it affects the joint structures The dietary management is discussed in Chapter 11 The patient with scurvy usually complains of pain in the legs The problem is more common in children than in adults In children there may be sub periosteal hemorrhages with swelling and tenderness of the long bones Hemorrhage occurs in and about the knee and ankle joints, causing swell ing, at times the hemorrhage may not be obvious to the physician This occurs in only a small proportion of patients with clinical scurvy The pain is severe but it may wax and wane quickly, and only once have I seen flexion deformities of the knee due to this condition

Pellagra and Beriberi —Muscle pain and stiffness, accompanied by cramps and tenderness, may be common, but joint disturbances or arthritis *per se* does not develop in these conditions

Postmenopausal senile osteoporosis of the spine may be confused with spondylitis or degenerative joint disease of the spine, but here radiographic study will soon reveal the true diagnosis Senile osteoporosis requires a high protein diet adequate calcium intake, and small amounts of vitamin D (2000 units daily) to increase calcium absorption The administration of male hormone and estrogens leads to increased deposition of protein matrix thus enhancing bone recalcification

The term *rheumatism* indicates all the aches and pains of the musculo skeletal system which cannot be more accurately diagnosed as bursitis, rheumatoid arthritis, gout, etc Many such syndromes are of psychogenic origin while others are manifestations of an organic nature which we do not as yet understand I do not believe that any specific diet is useful in these conditions

Neuropathic Arthropathy—Charcot s Joints —Rapid degenerative changes in joints may be due to lack of trophic impulses, as Charcot postulated, or due to microtraumata resulting from the loss of the normal proprioceptive senses, the latter theory is more widely accepted Clinical conditions which may produce this type of joint disease are tabes dorsalis, syringomyelia, trauma to spinal cord or posterior nerve roots, cord tumors, spinal caries from tuberculosis, malignant tumors, myelitis, poliomyelitis leprosy, yaws, diabetic neuritis toxic neuritis, and hemiplegic states

Dietary regimens are not helpful in these conditions except to reduce body weight and improve nutrition of and to the peripheral nerves and joint structures

Allergic arthritis as such does not exist, but joint inflammation and urticaria have been reproduced in certain patients by certain foods or other substances The elimination of the allergens from the diet is ob viously indicated in the treatment of such patients

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Chapter 29

Nutrition and Diseases of the Skin

By W. A. Krehl and Carroll S. Wright

Introduction.—What is so desired as a clear, soft, unblemished skin of fine, smooth texture—not too dry or too moist? "The skin you love to touch" is the goal for which millions are spent each year for myriad kinds of cosmetics, soaps, salves, vibrators, mud packs, *etc.* ad nauseum.

From primitive times, man has related the gloss and sheen of the hair coat and skin of his pets and herds with good dietary practices and good general health. In experimental nutrition studies, a change in the hair coat and skin of animals has often been the first and most outstanding feature of deficiency disease. Unfortunately, these skin and hair changes are so nonspecific, that they rarely permit a specific diagnosis of an isolated nutritional deficiency. However, because these skin changes have appeared with poor diet, dermatologists have naturally been much influenced by the use of special diets, vitamins and minerals in nearly every conceivable dosage level and combination in an attempt to manage and treat skin diseases. Since accurate diagnosis is difficult under such conditions and since many skin diseases are of unknown etiology, much of this form of therapy has been doomed to failure and, indeed, has tended to place the *role of nutrition in the therapy of skin disease in disrepute.*

While dermatoses related to dietary deficiency states can appear on any part of the body, they do for the most part tend to be located over areas of irritation or excessive stimulation. Lesions are most apt to appear on the backs of the hands, on the front and backs of the wrists, on the elbows, over the face, around the neck, under the breasts, over the knees and feet, and in the perianal region. These lesions are often bilaterally symmetrical and tend to be separated from healthier appearing skin by a sharp line of demarcation. They are generally accompanied by burning, itching, and pain.[1]

The skin area in the average adult is about 1.75 square meters of a tough, yet resilient, double layered structure of skin which is the principal line of defense against the entrance of foreign substances and protects against almost every conceivable physical and chemical stress. When damaged, it has remarkable ability to repair itself, thus reflecting its dynamic metabolic activity. Through its sweat glands and blood vessels, the skin provides the principal means by which the body heat is regulated and through its nerve endings permits sensation of contact with the external environment perceiving heat, cold, pain and other stimuli. The skin also reflects the emotions, such as embarrassment, fear, anger, anxiety and, unfortunately, a person's age as well. We are even individualized by characteristic skin markings—our fingerprints.

A brief review of the structure and physiology of the skin may be helpful in understanding the changes that take place in skin diseases[2,3]. The skin is composed of three principal layers: (a) epidermis, (b) corium (dermis or true skin), and (c) the subcutaneous tissue.

The epidermis is a thin layer averaging about 0.2 mm. in thickness, in which the greatest metabolic activity of the skin is located. From the outside inward, the epidermis is composed of cell layers, i.e. (a) stratum corneum, (b) stratum granulosum, (c) prickle cell layer, and (d) the basal cell layer. Melanocyte cells, responsible for the production of skin pigment, are found in the basal cell layer. The epidermis overlies the corium or dermis in a wave-like pattern. The principal metabolic activity of the epidermis is the production of the protein keratin, which is the chief component of the layer stratum corneum. Keratin by its toughness, elasticity and resistance to chemical change, provides great protection. It is structurally integrated into the flat, shrunken non nucleated dead cells of the stratum corneum. The process of keratinization is therefore concerned with the production of keratin and the gradual elaboration and replacement of the stratum corneum from the basal cell layer of the epidermis. This response is continuous and may vary with the stimuli on the epidermis.

There are two kinds of skin appendages derived from the epidermis: (a) glandular, i.e. apocrine and eccrine sweat glands, and sebaceous glands and (b) keratinized structures, i.e. the hair follicles and hair and the nails.

The corium or secondary protective layer supports the vascular bed and peripheral nerves of the skin and the epidermal appendages. The corium is also a large potential storehouse for water, blood and electrolytes. This is well exemplified in the individual with edema.

The subcutaneous tissue provides further support and is an excellent heat insulator, a good shock absorber, and a storehouse of calories in the form of fat.

Protein Deficiency.—The proteins of plasma, especially albumin, exert an essential osmotic influence on preventing the loss of water from the vascular system. Any clinical circumstance in which the plasma level of albumin falls much below 2.5 grams per 100 cc. leads to the development of edema. An adequate level of dietary protein of good biological value should be achieved in any therapeutic regimen in an edematous person with hypoalbuminemia. However in severe cirrhosis of the liver where the ability to metabolize amino acids is seriously impaired, protein must be used with great caution to prevent the development of hepatic coma.

It has also been shown that long exposure to experimental diets low in protein, results in extensive skin changes. These changes are characterized by dryness, scaliness, inelasticity, and a gray, pallid appearance suggestive of old age. Also noticed, is a blotchy, dirty, brownish pigmentation, which may appear anywhere on the body but is generally most often seen on the face[4].

Widespread throughout the technically underdeveloped areas of the world, and especially in children between the ages of 1 to 4, is a protein deficiency manifested in the extreme by the disease known as kwashiorkor. This disease is characterized by faulty growth, marked liver enlargement

with fatty infiltration, gastrointestinal disturbances, including diarrhea, and extensive skin changes with hypopigmentation and dryness of the hair and skin.[5] Therapy for this disease is an adequate amount of protein particularly of animal origin, although mixtures of selected vegetable protein prove quite satisfactory. The important question here is how to get into the basic diet of millions of people enough protein of proper nutritional value. This is undoubtedly the single most challenging problem to our nutritionists, economists, agriculturists, and public health workers.

A recent development in the nutritional therapy of a disease involving skin has to do with a congenital or genetic defect in phenylalanine metabolism. In phenylpyruvicoligophrenia, one sees marked skin changes characterized by eczematous skin eruptions and evidence of inadequate melanin formation. In this condition, a genetically controlled metabolic block limits the conversion of the amino acid phenylaline to tyrosine, and is accompanied by an increased urinary excretion of phenylpyruvic acid. A much more serious defect, however, in patients with this disease is the early development of feeble mindedness. Diets that are restricted in phenylalanine and supplemented with tyrosine have been shown to be remarkably effective in correcting many of the manifestations of this disease, but it must be emphasized that early diagnosis and treatment is essential if feeble mindedness is to be prevented.

Lipids.—Several types of skin lesions, eczematous in character have been associated with the long term consumption of diets low in fat.[6] It has also been noted that individuals who have excessive fat losses associated with idiopathic steatorrhea frequently have erythematous eczematous lesions.[7] Difficulties arise however in attempting to correlate these skin lesions with any specific biochemical abnormality. For example, while there is no significant difference between the level of total blood lipids of eczematous and non-eczematous infants, it has been shown that the amount of unsaturated fatty acids is considerably lower in eczematous infants, particularly the levels of arachidonic and linoleic acid.[8] This observation has encouraged the use of fats and oils rich in these two substances in the treatment of eczema in infants—unfortunately, not with uniformly good results.

Studies on the disease phrynoderma or hyperkeratosis follicularis, have shown that the increased incidence of this disease is correlated with a lowered intake of essential fatty acids. While vitamin A has often been proposed in the treatment of this disease it has been effective in relatively few cases. However, recent studies in India where this disease is common have shown that the administration of raw linseed oil or linoleic acid produced marked clinical improvement in two to four weeks and cured many patients in four to twenty-four weeks.[9] Even better results were obtained when pyridoxine was combined with the essential fatty acid therapy of phrynoderma.

In view of the fact that vitamin A in huge doses has been used in the treatment of certain dermatological lesions, a word of caution must be raised. Doses of 100 000 to 300,000 units per day may produce signs and symptoms of vitamin A intoxication, which in fact resemble the lesions of vitamin A deficiency as far as the skin is concerned. In addition bone changes take place, which reduce their density and make them brittle.

Obesity and Skin Disease —The obese patient seems to be excessively plagued with skin disorders With obesity, one has excessive fat folds with resultant intertrigo caused primarily by friction between the skin surfaces and by the maceration of the skin from accumulated moisture in these folds These changes often lead to infection, particularly with staphylococcal organisms or to fungus diseases, such as, dermatophytosis and moniliasis In addition, many obese patients activate a latent diabetic tendency with all of the accompanying dermatoses associated with diabetes Obese people because of their thick subcutaneous layers of fat, tend to become overheated easily and sweat more profusely This produces undesirable effects on normal skin, exaggerating areas of inflammation and skin rashes Prickly heat or miliaria rubra is a commonly recognized evidence of sweat retention Obviously the therapy for this problem is correction of obesity by decreased caloric intake and increased exercise (see Chapter 30A)

VITAMINS AND SKIN DISEASE

The search for vitamins has always captured the imagination of the research scientist and because deficiencies of these substances were so often associated with skin and hair changes in experimental animals, it was an easy transition from animals to man by dermatologists and physicians eager to treat difficult dermatological problems Hence vitamins in every form combination and dosage level have been used in the treatment of skin diseases with a great variety of results These are characterized mostly by their inconsistency The question most often raised is the need for vitamins beyond that ordinarily present in a well balanced diet Frankly, there is no easy answer to this question but it should be remembered that in skin disease as with disease in general, there is tissue pathology and presumably accompanying abnormal metabolism Certainly adequate vitamin intake must be insured which is most easily done by appropriate vitamin supplementation Danger lies however, in overzealous specific claims for 'skin cures effected by vitamins since many dermatological problems improve without therapy and for no known reason Certainly claims for vitamin therapy must be made only after the closest control of experimental or clinical studies and the most conservative judgment must be exercised

Vitamin A —Since vitamin A is intimately concerned in the maintenance of normal cell structure, one of the most characteristic changes seen in vitamin A deficiency is disintegration of epithelial surfaces followed by their replacement with a keratinized stratified epithelium

In man, lack of vitamin A[10] may result in dryness scaliness, furunculosis, and abscesses of the scalp and in bleaching drying out or loss of the hair The follicular lesions which are most helpful in establishing diagnosis, vary in size, the maximum diameter being 5 mm They are hard, deeply pigmented and surrounded by a zone of pigmentation The center of the lesion the papule is a scaly pointed plug of keratinized epithelium which if pressed out, leaves a crater Though comedones are common on the face, the keratinized lesions do not occur there, hence the two are never

associated, though both respond promptly to treatment with vitamin A Histologic examination shows hyperplasia and hyperkeratinization of the related epithelium around the hair follicles, together with metaplastic changes of the sweat ducts and degeneration of the glands, accounting for the dryness of the skin

Frazier and Hu[11] have described a skin eruption occurring in Chinese soldiers which they consider typical of vitamin A deficiency The skin first becomes dry and rough, then spinous papules appear at the sites of the hair follicles—first on the anterolateral surfaces of the thighs and the posterolateral aspects of the arms, at last the eruptions occur over the entire integument In debilitated patients and in those with poor habits of personal cleanliness, pustules may develop Occasionally, atrophic ulcers appear Microscopic study of the tissues shows hyperkeratinization of the epidermis and follicles together with metaplasia of the sweat duct epithelium into that of the squamous type Proper diet causes a gradual improvement

As might be anticipated, those skin lesions which are associated with a deficient intake of vitamin A respond to therapy with this vitamin

The use of vitamin A in the treatment of other diseases associated with excessive keratinization, particularly those involving the hair follicle, have not always yielded consistently beneficial results This therapy has shown to be of some therapeutic value, however, in the treatment of pityriasis rubra pilaris and Darier's disease While such treatment may provide symptomatic improvement, it is rarely curative Again, as pointed out above, one must warn against the long term dosage of massive amounts of vitamin A[1] This is a potentially toxic material

Of interest also, is the fact that an excessive intake of pro-vitamin A, carotene produces a yellowish discoloration of the skin and carotenemia This, at first glance, may be confused with jaundice It represents an inability of the body to convert carotene rapidly enough to vitamin A in the face of a large carotene intake

Vitamin B Complex Deficiencies —Experimental animal studies in which deficiencies of nearly all of the B complex vitamins have been established are all associated with some skin or hair changes ranging from mild to severe The correlation between these changes noted in animals and various dermatological lesions seen in man, remains unclear Riboflavin, niacin pyridoxine and possibly pantothenic acid are the members of the B complex group of vitamins that have clinical dermatological significance for man

Riboflavin —The symptoms of riboflavin deficiency may be divided into three groups—oral, cutaneous and ocular [13] The oral changes are angular stomatitis and cheilosis and are not alone characteristic of riboflavin deficiency other possible causes of these lesions must be ruled out Tongue changes are noted in riboflavin deficiency, particularly characterized by purplish or magenta glossitis [14] The dermatitis of riboflavin deficiency is primarily a seborrheic dermatitis with many fine greasy scales on an erythematous base

Of considerable interest are the results of studies on nutrition in the Far East by Pollack and his co-workers [15] These studies, carried out on

Chinese Nationalist Army troops on Formosa, clearly indicate a very high incidence of riboflavin deficiency and an interesting syndrome called the oral genital syndrome has been described A very high incidence of scrotal dermatitis was observed in those individuals who also had angular stomatitis cheilosis, magenta tongue, and nasolabial seborrhea When the biochemical findings in blood and urine were correlated with the clinical findings in the oral-genital syndrome it was evident that a riboflavin deficiency was involved Niacin deficiency was also noted in significant numbers in this study Enrichment of the rice in the diet with riboflavin and niacin rapidly eliminated the signs attributable to the deficiency of these vitamins It is now becoming more evident from nutrition surveys conducted through many areas of the world that riboflavin deficiency is one of the most common seen

Niacin Deficiency—Pellagra —The earliest symptoms of pellagra may involve either the skin or the gastrointestinal tract Premonitory evidence of skin involvement may appear as a temporary redness like that of sunburn it clears up without a trace only to return later in severer degree Earliest lesions are usually macular, of a light or dark red color but these coalesce and form a dark red or puplish eruption followed by desquamation The areas involved are those of friction and exposure The face, neck hands forearms and feet are the usual sites This early eruption may be accompanied by considerable swelling of the involved parts In severe cases bullæ may be present but usually these dry up leaving crusts, though they may of course become infected Ulceration has been known to occur A highly characteristic feature of the erythema and subsequent pigmentation is the occurrence of sharp margination of the wrist or forearm producing the so called ' pellagrous glove (Fig 61) The skin manifestations present three stages (1) congestion (2) thickening and pigmentation (3) atrophic thinning Subjective symptoms are usually slight, and they consist chiefly of a burning sensation rather than an itching

The mucous membranes are also involved The tongue becomes swollen and denuded and is often brilliant red in color The buccal mucous membrane may, in severe cases have a similar appearance the redness may at times extend to the lips too Sometimes the oral commissures become fissured

Thousands of pellagrous patients have now been treated with niacin or niacinamide Doses up to 1,000 mg daily may be safely administered, although the average dose is 100 mg t i d In a day or two the redness of the oral pharyngeal and vaginal mucous membranes is reduced nausea vomiting, and excessive salivation decrease and bowel movements become normal Unless the continuity of the skin is broken the acute red lesions fade rapidly The acute mental symptoms varying from confusion to delirium and mania, usually disappear quickly The addition of vitamin B_1 is necessary to improve symptoms due to involvement of the peripheral nervous system Riboflavin may be required if there is clinical evidence of an associated riboflavin deficiency

Diets in which corn predominates are prone to lead to niacin deficiency and pellagra especially if these diets are inadequate in proteins that contain tryptophane [16] The niacin requirement is significantly affected by the

amount of tryptophane in the diet since this amino acid is metabolically converted by the body to niacin The approximate dietary replacement ratio is 50 or 60 mg of tryptophane to 1 mg of niacin

Another interesting aspect of nicotinic acid therapy is the dermatological effect of producing a marked cutaneous vasodilatation with extensive flushing of the skin This characteristic is not shared by nicotinamide

Vitamin B-6 —The effects of pyridoxine deficiency in a number of dermatoses have been studied and it is reported that certain kinds of eczema, particularly eczema of the seborrheic type, may improve, after having

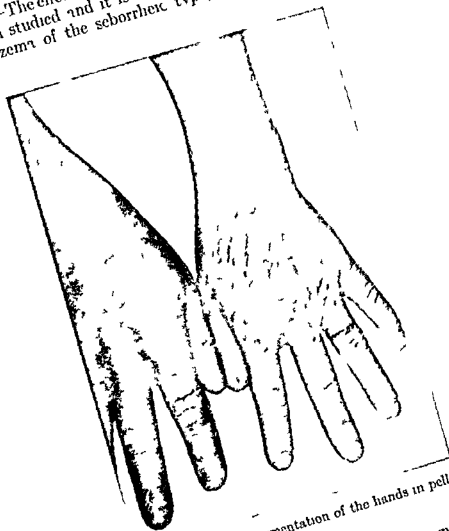


Fig 61 —Glove-like pigmentation of the hands in pellagra

failed to respond to local treatment, when pyridoxine is given intravenously or subcutaneously in rather large doses of 24 to 50 mg [17] Pyridoxine deficiency has been produced in human subjects by the use of pyridoxine antagonists and in association with this deficiency there is seen a seborrhea like lesion about the eyes, nasal labial fold and mouth, with extension to the eyebrows and skin behind the ears Many of these cases of seborrheic dermatitis responded well to the local application of pyridoxine in an ointment base, while but little effect was noted when the vitamin was given orally or parenterally [18]

OTHER VITAMINS

Vitamin C.—In vitamin C deficiency there is impairment of the structure of the ground substance of the connective tissue and in scurvy the skin may show secondary changes, such as petechial hemorrhage and inelasticity. Ascorbic acid is also concerned with the metabolism of the amino acids tyrosine and phenylalanine, which are precursor substances for the formation of the melanin pigments of the skin.

Therapy with vitamin C has been proposed for a variety of skin diseases, such as allergic contact dermatitis, atopic dermatitis, psoriasis, and acne vulgaris. Unless there is associated vitamin C deficiency no benefit is derived from the use of this vitamin in the specific treatment of the above conditions.

Pantothenic Acid, Inositol, p-Amino Benzoic Acid and Biotin.—Experiments reported by Woolley[19] have shown that pantothenic acid has an influence on the growth of hair. It has also been shown that a deficiency of pantothenic acid is a factor in the graying of hair and that pantothenic acid improved the skin and decreased graying of the fur of experimental animals.[20, 21] Unna, Richards and Sampson[22] have found that black rats fed a synthetic diet deficient in pantothenic acid become gray in from four to six weeks. Pantothenic acid at a level of 100 mg. a day will prevent or cure this condition. On the other hand, Williams[23] found pantothenic acid to be without effect on the graying of hair. There is no evidence that pantothenic acid acts in human beings as it seems to act in various animals. Spies and his co-workers[24] believe, however, that pantothenic acid and riboflavin are intimately associated in their behavior, and it is true that patients with cheilosis and other manifestations of riboflavin deficiency have shown marked improvement when given pantothenic acid. Though the human requirements and possible therapeutic doses are unknown, it is known that as much as 100 mg. daily is well tolerated.

Little is known about inositol; its relation to human nutrition is still a subject for investigation. Considerable interest has been aroused by the investigations of Woolley,[25] who has shown that inositol will cure alopecia in mice.

Thirty-three patients with lupus erythematosus were given 1 to 4 gm. of para-amino benzoic acid (PABA) at two- to three-hour intervals by Zarofonetis.[26] Two of 10 with chronic discoid lupus showed no improvement, 1 patient had a poor response and 7 good to excellent responses. Improvement occurred in all of 7 patients with scleroderma, the sclerodermatous areas gradually softening and becoming thinner and more pliable. PABA produced improvement in 5 patients with dermatitis herpetiformis. Toxic hepatitis, drug fever and nausea and vomiting may occasionally result from PABA and much more careful work must be done before any serious recommendations can be made for its use in dermatological conditions.

Biotin-deficient rats develop marked loss of hair with erythema of the underlying skin. Marked peri-orbital hair loss is also noted which may represent in part a complication from inositol deficiency. No counterpart deficiency has been demonstrated in man.

Vitamin K, Vitamin E and Vitamin D.—A deficiency of vitamin K resulting in impaired synthesis of prothrombin may result in a cutaneous purpura reflecting impairment of the coagulation mechanism.

No clear-cut cutaneous manifestations are associated with vitamin E deficiency. Indeed, only recently has this vitamin been shown to be essential for man. As the intake of essential fatty acids increases the need for a greater dietary supply of vitamin E becomes evident. Many oils that are recommended in substantial amounts in the management of certain skin diseases may increase the need for vitamin E in the diet. Fortunately, most vegetable oils are in fact good sources of vitamin E.*

Vitamin D is of interest to the dermatologist since sunlight converts vitamin D precursors in the skin to the active form of the vitamin. Vitamin D was at one time used successfully in the treatment of lupus vulgaris, but this therapy has been abandoned in favor of the more specific anti-tuberculosis drugs. As with vitamin A, vitamin D given in continued large doses may cause toxic manifestations with extensive soft tissue calcification. It must, therefore, be used with caution.

Side Effects of Vitamin Therapy.—Certain undesirable cutaneous side effects may be associated with the use of vitamins. These are for the most part allergic in character. Vitamin B may cause urticaria, angio-neurotic edema, pruritis and contact dermatitis. Niacin produces marked erythema, peripheral vasodilation and pruritis. This is quite a common reaction noted in patients who are given niacin to attempt to lower the blood cholesterol. Cutaneous reaction to niacin, interestingly, is not seen with niacinamide which, incidentally, does not lower blood cholesterol levels.

Vitamin B_{12}, which contains cobalt, may cause reactions in cobalt sensitive patients especially when given by the parenteral route.

As might be expected, vitamins like other chemical substances might be anticipated to cause allergic reactions with dermatological manifestations in a certain number of individuals. Fortunately, the incidence is quite insignificant.

DIET AND OTHER DERMATOLOGICAL PROBLEMS

Allergy.—Food allergy may be the cause of many skin lesions, including atopic dermatitis, urticaria, infantile dermatitis and eczema.[27]

The allergenic properties of a food depend on the nature of the food, the quantity and concentration of the food in the diet, and the duration of exposure to the allergenic substance. In addition, one must consider the problem of host susceptibility. A family with an allergic background should be considered an important danger signal indicating special care in the feeding of infants and small children, particularly during the period of "physiologic, immunologic immaturity."

Food allergens may enter the body by way of the gastrointestinal tract and derangements of the gastrointestinal system are among the prime factors leading to food allergy.

Almost all foods and beverages have at one time or another been in

*Vitamin E has been considered by Food and Drug Administration, Dept. Health, Education and Welfare, as an essential nutrient for man. (Federal Register, October 1959.)

incriminated as being allergenic but those that are most considered are unaltered egg protein, milk protein, fish and seafood, wheat corn, tomatoes, spinach, cabbage, asparagus rhubarb celery, onion, garlic and citrus fruits and juices

When the allergenic role of a food has been established, it may be corrected by (*a*) elimination of the food in question or (*b*) by specific desensitization Unfortunately, food elimination as a means of therapy may lead to rather bizarre and unusual dietary patterns There must be careful supervision of the diet under these circumstances in order to insure adequate and balanced nutrition

To indicate the really great difficulties and complexities of dermatology, two important dermatological problems with unknown etiology and for which there is no specific proved therapy deserve mention These are psoriasis and acne vulgaris These are also selected because diet has been so extensively involved in their management

Xanthoma —Xanthoma of the skin, characterized by round or oval, solid firm reddish brown papules are often distributed over the buttocks, elbows and knees and may be seen in patients with diabetes or hypercholesterolemia from almost any cause a familial form of xanthomatoses is also known Analyses of these xanthomatous lesions show an excess of fatty acids, cholesterol and other lipid substances Their deposition probably reflects the high cholesterol content of blood and other lipids in patients with disordered fat metabolism such as may be seen in poorly controlled diabetics and in patients with other abnormalities of lipid metabolism some of which may be familial in origin Some observers have reported the marked improvement and even disappearance of these xanthoma when the patient is placed on a low fat diet for long periods of time [28] Unfortunately, this is often very difficult to achieve and results are most discouraging

Psoriasis —Psoriasis is a chronic inflammatory skin disease characterized by the development of reddish, erythematous patches covered with raised, silvery-white dried scales Cracking and fissuring of the skin in the extensive psoriatic area is quite common The disease effects primarily the extensor surfaces of the body and the scalp although it may be very widely disseminated

While such patients have failed to show any clear-cut metabolic disturbance as the underlying cause of this dermatitis some interesting studies have been conducted For many years it has been demonstrated that a diet free from fat or very low in protein is moderately therapeutically effective in the treatment of psoriasis [29] Schamberg[30,31] has been the outstanding proponent of the low protein diet and he has indicated that psoriatic individuals give definite signs of abnormal nitrogen retention Patients with psoriasis placed on diets containing no more than 4 or 5 gm of nitrogen per day, with an adequate caloric intake were able to maintain their weight and experienced a gradual disappearance of the lesions of this disease Unfortunately when this very restricted dietary regimen is discontinued the disease returns

Recent findings have shown that the psoriatic scales containing keratin-like protein have an unusually high content of sulfur amino acids In this connection it is worth noting that the standard therapy of psoriasis

with coal tar and ultraviolet light are both known to disrupt the metabolism of the sulfhydryl group and may provide a clue to understanding and therapy of this disease It has also been reported that there is an interesting relationship between decreased urinary secretion of sulfur and of ascorbic acid in patients with psoriasis [3] Experiments with diets containing a maximum of 250 mg of sulfur per day in patients for periods of several months have yielded inconsistent results

Attempts are now in progress to feed psoriatic patients for extended periods on purely synthetic diets with known intakes of amino acids and other nutrients By such an approach, the role of sulfur amino acid metabolism in psoriasis may be clarified

Acne Vulgaris —Acne vulgaris is a chronic inflammatory disease of the sebaceous glands and the pylosebaceous structures of the skin, and is almost always associated with seborrhea This is predominantly a dermatological disease of youth, particularly teenage youth and associated with it are all of the emotional and psychological factors so prevalent in this age group It is a rather common clinical experience that gross dietary indiscretion, particularly in the form of taking too much cake, candy, ice cream and chocolates aggravates an existing acne and strongly suggests that the skin condition may be associated with a disturbance of carbohydrate metabolism [33] Not all agree on this and, in fact, improvement has been reported in patients taking a high carbohydrate diet [34]

It is also thought that acne is made worse by diets high in fat Unfortunately, low fat diets have not been particularly effective in the management of this problem It may well be that the principal effect of high fat diets is to permit excessive weight gain in children with acne, who are often withdrawn, quiet and relatively inactive because of the emotional trauma that is associated with the stigma of this disease It has been pointed out that the diet of the Eskimo is mostly fat and protein, but Eskimos have relatively little or no acne One cannot doubt that psychoneurogenous factors play a significant role in producing exacerbation of this disease In addition, fatigue and exhaustion are often predisposing factors

In view of the fact that we have no specific knowledge as to the cause or treatment of acne, it seems most reasonable to place persons with this disease on a well-balanced diet, which does not contribute an excessive amount of calories, so that weight gain is not excessive Such a diet should contribute all of the food nutrients in the recommended daily allowances Perhaps most important of all, the child or individual with this disease as with all difficult dermatological diseases, must have the necessary psychological lift from the physician and from his friends and family to permit him to learn to live with his disease and function as much like a normal individual as possible Again, often easier said than done

SUMMARY

There is little doubt that dietary deficiency, whether primary or conditioned, may be associated with dermatological lesions which can respond to specific therapy with vitamins or unusual diets

Dermatoses are certainly associated with obesity and since this is such a common problem in this country, therapy directed at weight reduction will probably provide the best management in related dermatological problems

The general dermatological changes associated with under nutrition, rather rare in this country, are extremely common in technically under-developed countries, and here improvement of the protein intake of the diet seems to be the most rational way of correcting this problem

Certainly, allergies to foods may produce dermatoses and such allergies should be ruled out if suspected either on the basis of family history or by history of the patient's food intake

It is extremely important that every patient presenting a dermatological problem should have a careful nutritional history, physical examination and if necessary, biochemical studies carried out to rule out any evidence of nutritional abnormality

For example, phenylpyruvicoligophrenia may be diagnosed simply and early by a simple test of the urine with ferric chloride Early diagnosis and therapy by restricting phenylalanine will produce most gratifying results

It must be remembered that the underlying defects related to dermatoses of unknown etiology may be the result of improper nutrition and metabolic error endured over very long periods of time Hence, their correction by diet or improved metabolism may require long and intensive therapy

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Chapter 30

A Obesity

By Michael G Wohl

INTRODUCTION AND DEFINITION

Obesity or excessive corpulence is not only unattractive it is a serious heath hazard It increases susceptibility to a number of diseases, among them gallbladder disease gout diabetes mellitus hypertension and possibly coronary atherosclerosis It may be considered to predispose to pulmonary emphysema and chronic bronchitis since it often results in interference with pulmonary ventilation It increases surgical risk And as insurance mortality statistics have forcibly indicated it reduces life expectancy

PATHOGENESIS

Obesity results from a positive energy balance that is from the daily ingestion of more calories than are expended for basal metabolic needs and physical activity or there may be decreased physical activity in the presence of a constant caloric intake The factors that affect energy imbalance however, are varied and complex

Factors and Theories —*Basal Metabolism* —That obesity is not caused by reduced heat production in the basal state is abundantly apparent from the reports of numerous investigators on basal metabolic rates in the obese Strouse Wang and Dye [1] for example found hardly any difference in heat production per square meter of body surface among the normal the underweight and the obese And Dr Ettelson and I found that only 8 of a series of 52 obese patients we studied in 1936 showed perceptibly low basal metabolic rates (minus 20 or lower) the rates indeed of 29 fell within the normal range, and those of 6 rose above 10 What is more as Strang and Evans[3] have pointed out if basal metabolic rate is estimated on the basis of active tissue mass rather than of surface area it will be found in obesity to be high rather than low Further Brozek and Keys have shown that basal metabolic rates calculated on the basis of lean body mass are high during the period of active fat accumulation but normal during the period of weight stabilization (static obesity) [4] It is evident that basal metabolic rate is of little use in elucidating the pathogenesis of obesity

Specific Dynamic Response to Food —Certain early investigators entertained the theory that in obese people the increase in heat production induced by the ingestion of food—on the average about 200 or 300 calories every twenty-four hours— was either below normal or wholly wanting and that this was the cause of obesity [5,6] It is impossible to say however what the importance of the specific dynamic action of food is in the pathogenesis

of obesity For, first of all, even if it were true that in the obese the specific dynamic response to food is less than normal or is wholly wanting, that would by no means account for the enormous discrepancies some observers have reported between alleged intake of food and change in weight[7] Secondly, the evidence of reliable investigators in this country indicates that there is no great difference in specific dynamic response to food between the mildly or even severely obese and normal persons[8]—which is what my own findings have led me to believe[9] The specific dynamic action of food is determined by the type of food, not by the "body that eats it"[10]

Psychogenic Factors—The importance of psychogenic factors in obesity is being more and more widely recognized Some people, for example, resort to overeating to alleviate tension, anxiety, worry, or frustration they are fat because life is hard, food is their liquor Hilda Bruch[11] has made several important contributions to the understanding of psychologic factors in the development of obesity in children Obesity in children, she tells us, is "intricately interwoven with the family interrelationship, the child's personality development and life experiences" If home offers a child little emotional security, he may make food a substitute for the love and sense of security he craves and needs An obese child is an unhappy child, overeating is his weapon against failure and disappointment The abnormal eating habits developed by such a child may persist into adult life and, combined with physical indolence, lead to obesity in maturity

Hamburger[12] lists four categories of overeating that lead to emotional obesity (1) overeating as a response to nonspecific emotional tensions, (2) overeating as a substitute gratification in intolerable life situations, (3) overeating as a symptom of underlying emotional illness, especially depression or hysteria, and (4) overeating as addiction to food A recent study on the psychiatric categories of eating difficulties in children has disclosed that there is a striking response in a child toward overeating or undereating in compliance with at times conscious or unconscious wishes communicated by one or both parents[1a] However, low energy expenditure (inactivity) must not be overlooked in 'emotional obesity"

Glucostatic Mechanism—Overeating of course, is not always directly associated with psychologic factors According to Mayer, the metabolic state of the organism "regulates" food intake, *i e*, adjusts intake to output This is mediated through the rate of passage of glucose into the cells of the ventromedial hypothalamic area—the seat of "feeding and satiety" centres When the availability of glucose to this area is diminished, the satiety centre is inhibited, releasing the feeding centre and hunger sensations ensue resulting in excessive food intake (Glucostatic mechanism)

During the period of active obesity in a group of women, Mayer and his associates[14] observed a lowering of nonfasting blood-sugar levels (increased tolerance to glucose and carbohydrate meal), whereas in women who had been obese for years and maintained their weight levels ("static obesity"), they observed rising blood-sugar levels after the test meal (low sugar tolerance) Fryer and associates failed to confirm Mayer's theory[15]

Heredity—Heredity has also been considered in the pathogenesis of obesity That obesity is more common in some families than in others is

well known, and it has been suggested that this is probably due to the transmission of an abnormal gene from parent to child, a gene acting through endocrine and neural channels Furthermore, a voracious appetite unaccompanied by the normal sense of satiety may be inherited and this in turn may be due to inherited aberrations in the mechanisms regulating appetite and the sense of satiety, mechanisms centered, presumably, in the hypothalamic area

Recent experiments with mice suggest that genetic factors may cause obesity through alterations in metabolism The "obese-hyperglycemia syndrome" of mice is characterized by extreme obesity, hypercholesterolemia and an insulin-resistant hyperglycemia The obesity a Mendelian recessive condition is connected with an increase in fat synthesis [16] But no proof is at hand that a similar mechanism is operative in human obesity It is not unreasonable, however, to state that familial tendency to gain weight might be due in some persons to familial food habits

Endocrinopathy — Intricate interrelationships exist among hereditary (constitutional) predisposition to obesity, the endocrine glands and the metabolic activity of the body Yet few obese patients show any clinical or laboratory evidence of endocrinopathy Mossberg, in a study of a large series of obese children found that not a single case was due to hypothyroidism In only 19 cases of obesity out of more than 500 could cerebral disease be implicated Furthermore he found that an inherited constitutional and familial factor served most of the cases as common denominator, the parents of obese children were more often obese than the parents of normal children And the more obese the child the more frequent the parental obesity, especially in the mother [19]

That obesity is at times closely connected with derangement of the endocrine system is generally known What is not known is *how*—which is after all, the point In primary hypogonadism in the male, as after castration (for instance, among members of the Russian religious sect *Skopzy*), the obesity is generalized, but there are conspicuous fat deposits in special regions— the lower abdomen the mons pubis the buttocks, the trochanters, the breasts and the outer sides of the upper eyelids [0] Another example is the "buffalo neck" and "moon-face obesity of Cushing's syndrome The obesity in this condition may actually represent an abnormal distribution of fat rather than an excessive fat accumulation

Obesity and Level of Activity —Decreased energy expenditure owing to diminished physical activity is an important cause of obesity in both man and laboratory animal [21] Pollack and associates have drawn attention to the decrease in caloric expenditure due to mechanization of life in recent years as a factor in development of obesity

Trauma —Traumatic obesity has been induced by hypothalamic lesion and by gold thioglucose injection in experimental animals

A Lesions of the Hypothalamus in Laboratory Animals —Many investigators have observed a connection between experimentally induced lesions of the hypothalamus in laboratory animals and obesity It was shown only recently for example, that experimentally induced lesions in the region of the ventromedian nuclei of the hypothalamus result in voracious appetite (hypothalamic hyperphagia) without corresponding increase in energy

output and the result of this is obesity But when the food intake of the animal with hypothalamic hyperphagia is kept equivalent to that of the control animal the former also maintains normal weight

Another set of "feeding centers" (the "appestat" of Jolliffe) are the lateral hypothalamic nuclei Stimulation of these nuclei results in a marked increase in food intake, on the other hand, destruction of the nuclei is followed by cessation of feeding[18] Thus there is experimental evidence for the existence of neural centers that regulate energy balance Whether such centers operate through the glucostatic mechanism of Mayer or in some other way is not established (See Chapter 5)

I *Regulatory Obesity* (No primary metabolic abnormality)
- A Increased caloric intake
  - 1 Organic central nervous system {injury / disease} of hypothalamus
  - 2 Functional psychologic
    - Neurotic overeating
    - Non neurotic overeating (cultural pattern)
- B Decreased caloric output
  - 1 Organic forced immobilization of convalescence
  - 2 *Functional* awkwardness in sports—adolescent day dreaming

II *Metabolic Obesity*
- A Neurologic *e g* lipodystrophy (rare) adiposa dolorosa (rare)
- B Hormonal hyperadrenocorticism (rare) adrenal carcinoma hypothyroidism (rare)
- C Enzymatic genetic obesity in mice obese-hyperglycemic syndrome

FIG 62 —Types of obesity according to mechanism (Harry H Gordon courtesy of Pediatrics Charles C Thomas, Publisher, modified from Van Itallie and Mayer)

B Injections of Gold Thioglucose in Mice —There is a variety of obesity induced by a single injection of gold thioglucose, a glucose analogue The obesity develops as a result of excessive food consumption after injection of the chemical This gold thioglucose obesity differs metabolically from the 'obese-hyperglycemia' syndrome in mice Mice injected with gold thioglucose have no hypercholesterolemia and show no rise in blood sugar after injection of the growth hormone No such counterpart state in man is known [3]

Summary —*Obesity is of multiple etiology The principal general cause* of the condition however is an imbalance between energy intake and energy output, the several factors causing this metabolic disorder result in a positive caloric balance

DIAGNOSIS

Standards —*If edema and ascites can be ruled out,* obesity may be diagnosed by inspection of the patient stripped and comparison of his body weight with the standards for his height, sex, and age (Table 135) It is to be borne in mind, however, that no ideal standards exist The patient's build and familial tendency the season of the year, and regional customs

must be taken into account What a patient should weigh between twenty-five and thirty years of age according to life insurance tables is probably what he should weigh, no matter what his adult age for optimal life expectancy A deviation of 10 per cent above this standard is considered indicative of overweight, a deviation of 25 per cent above it represents obesity The importance of differentiating between overweight and obesity is discussed by Keyes (See Chapter 1)

TABLE 135 —AVERAGE WEIGHTS OF MEN*

Graduated Weights (in indoor clothing) in Pounds

Height	*Age Groups* 15–16	17–19	20–24	25–29	30–39	40–49	50–59	60–69
5 0	98	113	122	128	131	134	136	133
1	102	116	125	131	134	137	139	136
2	107	119	128	134	137	140	142	139
3	112	123	132	138	141	144	145	142
4	117	127	136	141	145	148	149	146
5	122	131	139	144	149	152	153	150
6	127	135	142	148	153	156	157	154
7	132	139	145	151	157	161	162	159
8	137	143	149	155	161	165	166	163
9	142	147	153	159	165	169	170	168
10	146	151	157	163	170	174	175	173
11	150	155	161	167	174	178	180	178
6 0	154	160	166	172	179	183	185	183
1	159	164	170	177	183	187	189	188
2	164	168	174	182	188	192	194	193
3	169	172	178	186	193	197	199	198
4	*	176	181	190	199	203	205	204

AVERAGE WEIGHTS OF WOMEN

Graduated Weights (in indoor clothing) in Pounds

Height	*Age Groups* 15–16	17–19	20–24	25–29	30–39	40–49	50–59	60–69
4 10	97	99	102	107	115	122	125	127
11	100	102	105	110	117	124	127	129
5 0	103	105	108	113	120	127	130	131
1	107	109	112	116	123	130	133	134
2	111	113	115	119	126	133	136	137
3	114	116	118	122	129	136	140	141
4	117	120	121	125	132	140	144	145
5	121	124	125	129	135	143	148	149
6	125	127	129	133	139	147	152	153
7	128	130	132	136	142	151	156	157
8	132	134	136	140	146	155	160	161
9	136	138	140	144	150	159	164	165
10	*	142	144	148	154	164	169	*
11	*	147	149	153	159	169	174	*
6 0	*	152	154	158	164	174	180	*

*Average weights omitted in classes having too few cases

These new average weight tables were published by The Society of Actuaries in 1959 as a result of its massive study of body build The figures represent weights in ordinary indoor clothing and heights with shoes (From Build and Blood Pressure Study, 1959 Society of Actuaries Volume I)

Differentiation.—The differentiation of obesity into types according to patterns of fat distribution is often impossible, since one type may merge into another. Obesity has, however, been classified into android and gynoid types.[4] In android obesity, the excess fat is confined to the head, the neck, and the upper trunk (as often in Cushing's syndrome). The abdomen and mesentery may be secondarily involved. In gynoid obesity, the hips and thighs are chiefly involved (as often in hypogonadism).

An effort should be made to determine the underlying cause of obesity, to discover the emotional, hormonal, environmental, and organic factors affecting the patient.

Methods of Estimating Total Body Fat.—There are several ways of estimating fat and fatness: (1) by using standard height-weight tables, (2) by measuring subcutaneous fat (*a*) with calipers, to discover thickness of skin-fold, and (*b*) by *x*-ray of the soft tissues, to determine the thickness of the subcutaneous fat itself, (3) by estimating body density (since fat, per unit volume, is considerably lighter than other body constituents, the volume can be determined by weighing the patient totally submerged in water, from the data gained, "lean body mass" and total body fat are calculated with appropriate corrections for residual air in the lungs and the gastro-intestinal tract), and (4) by estimating total body water (on the dilution principle: since total body water, TBW, represents a constant fraction of 'lean body mass,' an estimate of it, if there is no edema or dehydration, and of total body weight provides a basis for calculating how much fat and how much nonfat mass the body holds).

For clinical use, measurement of skin fold thickness by the digital method (skin-fold pinch) and reference to standard age, sex, height, and weight tables will be found most practical.

Prevention.—Whenever a history of adiposity is obtained, prophylaxis is indicated. In such a case the patient should be guided in establishing proper eating habits and encouraged to take moderate regular exercise. This is especially important at puberty, after childbirth, and at the menopause. Furthermore, all patients convalescing from surgical operations or infectious diseases should be carefully watched, lest they develop excessive appetites and grow obese.

Treatment.—Every sound reducing plan is based, first, on the principle that a proper diet is essential for reduction of weight. Second, such a plan should provide for increasing and regulating the amount of exercise. In prescribing exercise for the obese, the physician must be cautious, indulgence in calisthenics ought to be limited, at first, to ten minutes night and morning, even walking, the best and safest of exercises, ought to be limited to several short walks a day or to daily walks of not more than 2 miles. However, it should be borne in mind that exercise alone will not bring about the desired weight loss unless assisted by dieting.

Dietary Correction and Reeducation in Eating Habits.—In order to lose weight the patient must take fewer calories than he uses. The diet should be practical, made up of ordinary every day foods tailored to the individual's cultural and economic circumstances. Special food fads are to be avoided.

Before putting a patient on a planned diet, it is essential to go into the patient's dietary habits, instruct him in elementary dietetics, provide him with information on essential foods and relative food energy values and teach him substitution foods as well as principles by which weight reduction can be achieved The substitution system divides all foods into six groups The foods within each group have the same energy value The patient can select any food in each group in amounts allowed him and exchange any food on one list for any other food of equal caloric value in the other lists If the patient fails to lose weight the physician who supervises the reduction regimen should point out errors in the patient's dietary habits and bolster his morale and his motivation to lose weight To save time a dietitian can carry out many of the educational tasks either with patients individually or in groups It has been our experience that success in achieving weight loss is in direct proportion to the patient's desire to lose weight and the extent of his understanding of the principles of weight loss and his knowledge of food values When satisfactory weight reduction has been accomplished the patient's new dietary habits, which are basic in the program, will enable him to adhere to a restricted diet and maintain his ideal weight

Composition of Diet —The diet should contain a protein component of 1 to 1^1 gm per kilogram of ideal body weight, protein being $\frac{2}{3}$ of animal origin, 1 to $1\frac{1}{2}$ gm carbohydrate (polysaccharide) per kilogram of ideal weight and enough fat to supply the rest of the daily caloric requirement One polyvitamin capsule daily should be prescribed as a margin of safety It is desirable that the patient eat slowly thus deriving more enjoyment from smaller quantities than he previously consumed to still hunger Physiologically, it is likely that the satiety mechanism needs time to take effect

It is obvious that the lower the caloric intake the more rapid the weight loss However too rapid weight loss in some patients may be attended by weakness, dizziness and increased tendency to anginal attacks Furthermore the patient on a severely restricted food intake is more likely to break his diet A diet of 1500 to 1700 calories is more acceptable by the patient it closely resembles normal eating pattern and will provide a more moderate weight loss—1 to 2 lbs per week

Computation of Total Daily Calories —There are approximately 3500 calories in each pound of excess stored fat To lose 1 lb per week it is necessary to subtract 500 calories from the daily caloric allowance for energy expenditure, for loss of 2 lbs per week 1000 fewer calories each day are consumed The caloric expenditure of persons may vary, depending on type and amount of activity height and frame and age of person Let us assume a man 40 years of age of median bone structure and 5 ft 7 inches tall and engaged in sedentary occupation He weighs 185 lbs, but his ideal weight is 161 lbs He consumes 2700 calories a day To lose 2 lbs per week his caloric intake must be reduced by 1000 calories daily *i e* daily intake 1700 calories To lose $2\frac{1}{2}$ lbs per week he will be put on 1500 calories a day *Water Elimination* To facilitate water elimination, ammonium chloride may be used Recently, we used chlorothiazide with good results (250 mg twice a day or three times daily)

TABLE 136.—THE EXCHANGE SYSTEM

The exchange system. The Exchange Lists are based on material in *Meal Planning with Exchange Lists* prepared by Committees of the American Diabetes Association, Inc. and The American Dietetic Association in cooperation with the Chronic Disease Program, Public Health Service, Department of Health, Education and Welfare.

LIST 1. MILK EXCHANGES

Carb.—12 gm. Protein—8 gm. Fat—10 gm. Calories—170

	Meas.
*Milk, whole	1 cup
Milk, evaporated	½ cup
*Milk, powdered	¼ cup
*Buttermilk	1 cup

*Add 2 fat exchanges if fat free.

LIST 2. VEGETABLE EXCHANGES

A.—These vegetables may be used as desired in ordinary amounts. Carbohydrates and Calories negligible.

	GREENS	
Asparagus		
Broccoli		Lettuce
Brussels Sprouts	Beet	Mushrooms
Cabbage	Chard	Okra
Cauliflower	Collard	Pepper
Celery	Dandelion	Radishes
Chicory	Kale	Rhubarb
Cucumbers	Mustard	Sauerkraut
Escarole	Spinach	String Beans, young
Eggplant	Turnip	Summer Squash
		Tomatoes

B.—Vegetables. 1 Serving equals ½ cup equals 100 grams.
Carb.—7 gm. Protein—2 gm. Calories—36

Beets	Peas, green	Squash, winter
Carrots	Pumpkin	Turnips
Onions	Rutabaga	

LIST 3. FRUIT EXCHANGES

Carbohydrate—10 gm., Calories—40

	Meas.
Apple	1 sm. (2" diam.)
Applesauce	½ cup
Apricots, fresh	2 medium
Apricots, dried	4 halves
Banana	½ small
Berries, Straw., Rasp., Black	1 cup
Blueberries	⅔ cup
Cantaloupe	¼ (6" diam.)
Cherries	10 large
Dates	2
Figs, fresh	2 large
Figs, dried	1 small
Grapefruit	½ small
Grapefruit Juice	½ cup
Grapes	12
Grape Juice	¼ cup
Honeydew Melon	⅛ (7" diam.)
Mango	½ small
Orange	1 small
Orange Juice	½ cup
Papaya	⅓ medium
Peach	1 medium
Pear	1 small
Pineapple	½ cup
Pineapple Juice	⅓ cup
Plums	2 medium
Prunes, dried	2 medium
Raisins	2 tbsp.
Tangerine	1 large
Watermelon	1 cup

These foods may be used as desired:

Coffee	
Tea	
Clear broth	Rennet tablets
ouillon (without fat)	Pickles, sour
elatin, unsweetened	Pickles, unsweetened dill
	Cranberries

TABLE 136 —*Continued*

LIST 4 BREAD EXCHANGES

Carbohydrate—15 gm Protein—2 gm, Calories—68

	Meas
Bread	1 slice
Biscuit, Roll	1 (2 diam)
Muffin	1 (2 diam)
Cornbread	1 (1½ cube)
Flour	2½ tbsp
Cereal cooked	½ cup
Cereal dry (flake & puffed)	¾ cup
Rice Grits cooked	½ cup
Spaghetti, Noodles etc cooked	½ cup
Crackers, graham (2½ sq)	2
Oyster	20 (½ cup)
Saltines (2 sq)	5
Soda (2½ sq)	3
Round thin (1½ diam)	6–8
Vegetables	
Beans & Peas dried cooked (lima navy split peas cowpeas etc)	½ cup
Baked Beans, no pork	¼ cup
Corn	⅓ cup
Parsnips	⅔ cup
Potatoes white baked boiled	1 (2 diam)
Potatoes, white mashed	½ cup
Potatoes, sweet or Yams	¼ cup
Sponge Cake plain	1 (1½ cube)
Ice Cream (Omit 2 fat exchanges)	½ cup

LIST 5 MEAT EXCHANGES

Protein—7 gm Fat—5 gm Calories—73

	Meas
Meat & Poultry (med fat) (beef, lamb, pork liver chicken etc)	1 oz
Cold Cuts (4½ sq ⅛ thick)	1 slice
Frankfurter	1 (8-9/lb)
Fish Cod Mackerel etc	1 oz
Salmon Tuna, Crab	¼ cup
Oysters Shrimp Clams	5 small
Sardines	3 medium
Cheese cheddar American	1 oz
Cottage	¼ cup
Egg	1
Peanut Butter*	2 tbsp

*Limit use or adjust carbohydrate

LIST 6 FAT EXCHANGES

Fat—5 gm Calories—45

	Meas
Butter or Margarine	1 tsp
Bacon crisp	1 slice
Cream light 20%	2 tbsp
Cream heavy 40%	1 tbsp
Cream Cheese	1 tbsp
French Dressing	1 tbsp
Mayonnaise	1 tsp
Oil or Cooking Fat	1 tsp
Nuts	6 small
Olives	5 small
Avocado	⅛ (4 diam)

The following seasonings may be used freely if desired

Chopped Parsley	Mint
Garlic	Onion
Celery	Nutmeg
Mustard	Cinnamon
Pepper and other spices	Saccharin
Lemon	Vinegar

Water Retention during Menstruation.—It is a common observation that women gain from 2 to 3 pounds during menstruation. This is due to the water retention that comes with that condition. During reducing, water retention may be exaggerated at the menstrual period, and the patient may cease to lose weight or actually gain weight. This may prove disheartening to the patient, especially since weight fluctuations owing to water retention may last for several weeks. Explanation of these facts may encourage the patient.

A Plan of Diets restricted to 1200, 1500 and 1700 calories and an Exchange System is given below.

SUGGESTED DIETS AND INSTRUCTIONS TO PATIENTS FOR WEIGHT REDUCTION*

The object of these diets is to eat less foods than you have been in the habit of eating, but the foods you do eat should be of a good quality and planned around three adequate meals a day. It is therefore necessary to choose foods of a wholesome nutritional value and eliminate those supplying largely calories because they are either too rich in fat or too generous in sugar or starch content. In order to do this, and still stay within the limits of the calories established, you must adhere to the diet carefully, not exceeding the quantities stated nor eating in between meals. It is equally important to eat all the foods outlined in your diet in the form of three meals in order to maintain your health and strength. If you follow your diet carefully, the body will consume its own fat for energy and a weight loss will result. The weight loss will be gradual but fairly steady. Bear in mind that there is no special food, no magic pill or mechanical device that will bring about loss of weight without cutting down the food intake.

1200 Calories

Breakfast

Fruit —½ cup orange juice
Bread —1 slice white or whole wheat
Egg —1 soft cooked
Milk —½ cup whole
Fat —1 tsp. butter
Tea or coffee as desired

Lunch

Fruit —½ cup applesauce
Bread —1 slice white or whole wheat
Meat —2½ slices luncheon meat
Milk —½ cup whole
Fat —½ tsp. butter
Vegetable 2A—sliced tomatoes on lettuce (as desired)
Vegetable 2B—½ cup cooked peas, green
Vegetable 2B—½ cup cooked carrots
Tea or coffee as desired

Breakfast

		From List
1 Fruit	Exchange	3
1 Bread	"	4
1 Egg	"	5
½ Milk		1
1 Fat		6
Tea or coffee as desired		

Lunch

1 Fruit	Exchange	3
1 Bread		4
2½ Meat		5
½ Milk		1
1 Fat	"	6
1 Vegetable		2A
Vegetable		2B
Tea or coffee as desired		

Dinner

Same as lunch

*From Nutrition Clinic, Philadelphia General Hospital. We are indebted to Miss Mary Alice Tkach for planning these diets.

1500 Calories

Breakfast	*Breakfast*		*From List*
Fruit —½ large grapefruit or 8 oz orange juice	2 Fruit	Exchanges	3
Cereal —¾ cup cornflakes	1 Cereal	"	4
Egg —1 poached	1 Egg	"	5
Milk —1 cup whole	1 Milk	"	1
Fat —1 tsp butter	1 Fat	"	6
Tea or coffee as desired	Tea or coffee as desired		

Clear broth or fat free bouillon as desired before lunch or dinner

Lunch	*Lunch*		
Fruit —4 medium plums	2 Fruit	Exchanges	3
Bread —1 slice white	1 Bread		4
Meat or fish—¾ cup tunafish	3 Meat or fish		5
Milk —½ cup whole	½ Milk	"	1
Fat —1 teaspoon mayonnaise	1 Fat		6
Vegetable 2*A*—as desired celery raw onions and lettuce—to make tunafish salad with 1 tsp mayonnaise	As desired vegetable from		2*A*
Vegetable 2*B*—½ cup beets, pickled or plain	1 Vegetable	Exchange	2*B*
Tea or coffee as desired	Tea or coffee as desired		

Dinner	*Dinner*		*From List*
Fruit (sliced) —½ small banana, 1 medium peach, Combined for dessert	2 Fruit	Exchanges	3
Potatoes—½ cup mashed	1 Potato		4
Meat —3 slices roast beef or ½ chicken breast	3 Meat		5
Milk —½ cup whole	½ Milk	"	1
Fat —1 tsp butter	1 Fat	"	6
Vegetable 2*A*—Tossed salad lettuce spinach celery radishes	As desired vegetable from		2*A*
Vegetable 2*B* —½ cup cooked carrots	1 Vegetable		2*B*
Tea or coffee as desired	Tea or coffee as desired		

1700 Calories

Breakfast	*Breakfast*		*From List*
Fruit —1 large tangerine or 2 prunes	1 Fruit	Exchange	3
Bread —1 slice white or whole wheat ½ cup oatmeal	2 Bread		4
Egg —1 soft cooked	1 Egg		5
Milk —1 cup whole	1 Milk		1
Fat —1 teaspoon butter	1 Fat		6
Tea or coffee as desired			

Lunch		*Lunch*		*From List*
Clear broth or fat free bouillon as desired before lunch or dinner				
Fruit	—1 small pear	1 Fruit	Exchange	3
Bread	—2 slices white or whole wheat	2 Bread	"	4
Meat	—3 slices American cheese or luncheon meat	3 Meat	"	5
Milk	—½ cup whole	½ Milk	"	1
Fat	—5 small olives 1 tsp mayonnaise for sandwich	2 Fat	"	6
Vegetable 2*A*	—as desired—lettuce for sandwich celery and carrot sticks to eat with olives as relish plate	2 A Vegetable as desired		
Vegetable 2*B*	—½ cup green peas	1 Vegetable		2*B*
Tea or coffee as desired				

Dinner		*Dinner*		*From List*
Fruit	—½ cup applesauce or 4 apricot halves	1 Fruit	Exchange	3
Bread	—1 biscuit average size ½ cup rice	2 Bread	"	4
Meat	—¼ lb steak	3 Meat	"	5
Milk	—½ cup whole	½ Milk	"	1
Fat	—1 teaspoon butter 1 tbsp —French dressing	2 Fat	"	6
Vegetable 2*A*	—½ cup coleslaw made with vinegar ½ cup string beans	2*A* vegetable as desired		
Vegetable 2*B*	—½ cup rutabagas or turnips	1 vegetable		2*B*
Tea or coffee as desired		Tea or coffee as desired		

Pharmaceutical Preparations —Drugs at best are a crutch to aid in adhering to a diet Weight cannot be lost without reducing food intake to the point where less is being eaten than the body is using up Drugs principally employed in the treatment of obesity are thyroid and amphetamine sulfate

Thyroid —Thyroid therapy in the form of desiccated and *L*-triiodothyronine is dangerous and should not be used unless the patient suffers from clinical hypothyroidism A low basal metabolic rate in an obese person is not sufficient evidence of the existence of hypothyroidism and is no basis for prescribing thyroid preparations

Amphetamine Sulfate —Amphetamine (5 to 10 mg half an hour before meals) has proved valuable in promoting weight reduction by depressing appetite and producing a sense of early satiety during meals This drug also makes the patient more ambitious and energetic and gives him a sense of well-being Dextrotary amphetamine sulfate is the drug of choice because of the low incidence of undesirable side-effects such as insomnia, nervousness and tachycardia, attendant upon its use On withdrawal of the drug the

side reactions (in whatever form), usually disappear. A combination of Dexedrine sulfate and amobarbital may often have value in curbing the appetite and lessening emotional distress.

Experience shows that, though amphetamine reduces the appetite, weight loss does not occur without dietary restriction.

Contraindications.—Amphetamine should not be used in patients sensitive to ephedrine-like compounds, in patients manifesting anxiety, hyperexcitability or undue restlessness or in patients with coronary disease or cardiac conditions in which vasoconstrictors are contraindicated. Some believe that amphetamine is contraindicated in the presence of hypertension, yet hypertensive obese patients are often those who need it most. Recently amphetamine sulfate was given to a group of hypertensive patients in combinations with phenobarbital; most showed a reduction in blood pressure and satisfactory loss of weight.

Other Anorexiant Drugs.—Two new appetite suppressing drugs have recently been introduced in the treatment of obesity. They are Preludin (phenmetrazine hydrochloride), 25 mg. three times a day, and Levonor (1-phenyl 2 aminopropane alginate) 5 mg. three times a day. The clinical experience with these new preparations is too limited to permit definitive evaluation.

Psychotherapy.—An effort should be made to investigate the obese patient's emotional life, his disappointments, fears and anxieties, particularly if he is a "nervous nibbler." He should be shown that his fears are exaggerated and that he reflects his difficulties in overeating, with resultant overweight. If it seems wise, the dangers of overweight may be pointed out to the patient in order to gain his cooperation. He should be encouraged and confidence instilled in him. The patient should be made aware that the physician has a true interest in his problems. For most patients superficial psychotherapy can be carried out by the physician who is responsible for the management of the patient. Formal psychotherapy for a large number of obese patients is a practical impossibility. In the Nutrition Clinic at the Philadelphia General Hospital, it has been our practice to refer to the psychiatrist for formal psychotherapy patients who have failed to lose weight on dietary management and supportive anorexient medication. Our experience has been that though about 50 per cent of the patients lose weight temporarily while under treatment, only a few continue to accept such treatment and only a small percentage continue to lose weight or maintain the level of weight loss. Our poor results may be entirely due to the kind of patients attending the clinic, patients in whom it was difficult to bring about a change of attitude about self and life.[5]

Group Therapy.—Getting groups of the obese together to talk about the problem of obesity is a form of therapy now widely used. Some patients without strong enough motivation on their own to adhere to a restricted diet may develop it through the group therapy. It is wise, however, to supplement group therapy with individual advice from a physician and a dietitian. The efficiency and effectiveness of a group method for weight reduction has recently been summarized by Harvey and Simmons.[6] "Discussion with participants, both those who lost significant amounts of

weight and those who didn't, as well as evidence from their histories of dieting, tends to support the impression that the group experience helped more than anything which had been offered in their previous attempts to lose weight This is revealed in the results which indicate that satisfactory weight loss can be expected from the majority of participants in groups"

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Chapter 30 (*Continued*)

B Undernutrition

By Francisco Gomez Mont

Introduction —Undeternutrition is a term usually applied to mean a condition in which the body weight is below the accepted standard[1] although it is preferable to include in this group, any condition in which there is a weight loss in process This condition can be the result of an insufficient diet or of excessive catabolic activity

Table 137 — Composition of the Diet Previous to Hospitalization* in Children

	Daily Intake	*Percentage of Normal*
Calories	700– 800	40–50
Protein	10– 30 gm	20–60
Fat	5– 15 gm	10–33
Carbohydrate	80– 140 gm	60 85
Calcium	100– 400 mgm	10–40
Phosphorus	200– 500 mgm	20–50
Iron	4– 8 mg	50–80
Vitamin A+	2000 I U	—
Thiamine+	400–1200 mcg	Sufficient
Riboflavin+	500–1500 mcg	Low
Nicotinic acid+	1– 2 5 mgm	Low
Ascorbic acid+	Less than 50 mgm	Low

*+Vitamins calculated for raw foods

Seventy five per cent of humanity is subject to a low calorie, low protein diet (Table 137 shows the nutrient content of a deficient diet eaten in a poor section of Mexico)[2] It is below the accepted standards in calcium phosphorus iron, riboflavin nicotinic acid ascorbic acid lysine tryptophan, isoleucine valine, threonine methionine and cystine The main source of calories is carbohydrates derived from corn and beans Milk, eggs and meat are rarely eaten and when they are the intake is very small A generally deficient diet is observed also in anorexic patients and in the course of hypermetabolic diseases, if the patients eat less of all the nutrients than the amounts required by the organism

During a period of food restriction the rate of activity of all the cells decreases and a clinical condition named undernutrition results This clinical picture is similar in all patients The presence of associated pathological states adds certain clinical features to the basic picture making it a complex condition[3,4] For this reason the terminology describing undernutrition has varied widely over the world Some of the more fre-

quently used names are Prekwashiorkor (Guatemala), kwashiorkor (Africa), atrepsia (Germany), hypotrophy (Mexico), malnutrition, pluricarential syndrome (Guatemala), shibi gachaki (Japan), starch dystrophy (Italy), protein malnutrition, mehlnährschaden (Germany), chronic severe malnutrition (Mexico) and marasmus.

On some occasions a deficiency disease may be primarily the result of a lack of one particular nutrient such as thiamine, niacin, ascorbic acid, etc. These are called "malnutrition syndromes" and are described in other sections of this book. Anorexia develops frequently in these patients and a picture of undernutrition is associated with them, forming a condition often indistinguishable from the disease due to a generally deficient diet.

In states of undernutrition a particular deficiency can become more clinically prominent than others under special conditions. Iron deficiency in menstruating undernourished women may produce hypochromic anemia as the outstanding pathological condition. In chronic diarrhea, calcium and vitamin D absorptions are decreased and osteomalacia results. These specific manifestations sometimes become so apparent that the disease is called by the name of its complications, but the complications are always related to the basic condition, a generally deficient food intake. The description of this entity is the purpose of this chapter.

CLINICAL PICTURE

General Considerations.—Two different clinical forms occur, one in children and one in adults. Children develop clinical signs easily when food restriction exists. At that period of life growth and maturation are the first functions to be affected. Adults are more resistant to food deprivation and, aside from weight loss, the effect on the reproductive organs is the most obvious clinical manifestation.

Three different clinical stages can be observed in undernourished patients. During the early stages of food restriction, there is great resistance to the deficiency.[3] The organism sacrifices only the most dispensable tissues and functions and maintains essential biological activities at a satisfactory level. This stage is termed the Compensated Stage. If undernutrition is continued for long periods of time or if additional stress factors appear, the severe form of undernutrition results. This is the Uncompensated Stage. Finally, when the patient recovers from malnutrition, the altered functions, revert to normal. Sometimes the recovery is so exaggerated as to produce certain abnormal clinical manifestations. This phase is called the Recovery Stage.

During the Uncompensated Stage of the disease it is important to consider three different groups of clinical signs.[4] (*a*) The Universal Signs due to the food restriction, which are in proportion to the severity of the disease. (*b*) The Circumstantial Signs which are related to the state of undernutrition but do not have any prognostic significance. These are largely dependent upon the speed of development to the severe state and on the age of the patient. Their recognition is important since they help in the diagnosis and offer a better understanding of the clinical condition of the patient. (*c*)

The Associated Signs which are due to intercurrent diseases acting as precipitating factors of the severe stage

A separate description of the clinical pictures in childhood and adulthood follows along with descriptions of the three stages of the disease in each case This is done because the different clinical manifestations have different prognostic and etiological significances

CHILDHOOD UNDERNUTRITION

The following is a brief summary of the condition as it is seen in Mexico This picture has been described by the Nutrition Department of the Children s Hospital of Mexico City [4-15]

Compensated Stage —Healthy children are at maximal anabolic activity, as manifested by growth and maturation They progress as fast as possible As a child gets older the speed of this process decreases until puberty is reached Underfed children show stunted growth, delayed maturation and slow weight gain They also show slow mental maturation delayed bone age and retarded puberty A decreased resistance to infection explains the high mortality rate observed in such children

Uncompensated Stage —This stage develops as a consequence of a superimposed factor usually an infectious disease a change in climatological conditions or a more severe food restriction The primary manifestation is diarrhea of variable degree and duration The accelerated intestinal transit decreases food absorption aggravates undernutrition and increases diarrhea Anxious mothers change the habitual foods and offer their children rice water and starches Diarrhea increases and aggravates the superimposed intestinal infection Digestive enzymes are decreased in the intestinal lumen, there is diminished fat absorption and diarrhea becomes permanent and severe A vicious circle is formed and the child proceeds into the severe form of uncompensated undernutrition

Universal Signs —Besides decreased stature and thinness children will show at this stage marked changes in water and electrolyte metabolism characterized by hemodilution decreased osmolarity and increased extra cellular and intracellular compartments Blood sodium and potassium are low acidosis is present and is of marked severity Polyuria is present even in the presence of decreased osmolarity of the blood The solute concentration of the urine is low If the subcutaneous fat has not disappeared during the previous undernutrition the child will show pitting edema If there is no subcutaneous fat left because of extreme emaciation edema will not be detected by the pitting sign in spite of an increased water content of the skin The electrolyte changes are of great prognostic significance Forty five per cent of the children presenting these changes will die during the first days of treatment In contrast only fifteen per cent of the children die when these changes are not present or are of not more than moderate intensity

Some other important universal signs include a decrease in serum albumin and an increase in serum gammaglobulins Usually the liver can not be felt and is decreased in size Some hepatomegaly due to diffuse fat infiltration, is observed at times

Circumstantial Signs —Characteristic skin changes are the most important of these The more frequent skin lesions are listed in Table 138

Hair acquires a grayish or reddish color This fact explains the name of Kwashiorkor (Red Hair) given to this condition in Africa The multi color scalp has been called "Flaghead"

TABLE 138 —INCIDENCE OF SKIN LESIONS[13] IN CHILDREN

Type of skin lesion	*Without clinical oedema (Percentage)*	*With clinical oedema (Percentage)*	't
Dry hyperchromic skin	90	94	
Very dry hyperchromic with mosaic appearance	38	46	
Follicular hyperkeratosis	20	26	
Hyperkeratosis palmaris et plantaris	48	37	
Fissures	3	6	
Seborrhoea	42	49	
Pellagrous erythema	13	47	4 94
Acute pellagrous dermatitis	18	40	2 94
Dyskeratotic hyperchromic lesions	50	83	3 00
Desquamating lesions in large flaps	8	21	2 48
Desquamating lesions in small flaps	13	37	3 81
Postdesquamation hypochromia	15	26	
Hyperchromia along capillary circulation	1 4	8	3 26
Crusty lesions suggesting post-purpuric lesions	6	11	
Purpuric lesions	24	28	
Perifolliculosis	1 4	11	3 07
Coldness and cyanosis of hands and feet	62	82	3 07
Marbleization	11	18	
Telangiectasis	1 4	6	
Gangrenous lesions and eschars	11	18	
Hypertrichosis	24	20	
'Wet cloth' sign	27	11	
Abdominal superficial circulation	6	7	

Age and previous degree of undernutrition will determine certain clinical characteristics Children below 18 months of age develop the severe picture when they are taken off breast feeding Stature is not particularly affected bone age and mental development are normal Electrolyte changes are most important at this age Clinical edema and skin changes are seldom observed *Children between 18 months and 6 years of age* show predominantly edema and skin lesions Children above six years of age generally present the compensated the disease Edema and skin changes are seen Child age are more resistant to developing changes

Associated Signs —Their recognition is important as they result from the associated pathological conditions that precipitate the onset of the severe form of the disease Shigellosis or amoebiasis in diarrhea steatorrhea in malabsorption syndrome or cystic disease of the pancreas, emesis with pyloric stenosis, hypoalbuminemia in a nephrotic patient, dyspnea, cough and fever with a respiratory infection, polyuria and hyperglycemia in diabetes etc

Associated with these signs and symptoms children will present mental confusion, hypotension vascular collapse and respiratory infections due to the aspiration of food or vomitus into the bronchi If they are left in these situations they will die

Recovery Stage —If the electrolyte and water disturbances are corrected and a normal diet is supplied there is a rapid return to normal growth and weight gain During this period children show some specific signs such as enlargement of the liver due to hydropic cell degeneration and ascitis due to portal hypertension Hypoalbuminemia improves Hypergamma globulinemia increases at the beginning and then tends to return to normal Cephalin cholesterol and thymol turbidity tests become positive The blood calcium decreases due to increased calcium deposition and tetany may appear Hypertrichosis and a Cushing-like-face sometimes appear suggesting some degree of adrenal hyperactivity It is important to recognize this stage as it means the process of recovery At the end of this period there is no residual manifestation of these conditions except the persistence of decreased stature a variable depending upon the age of onset and duration of the period for which growth became slow because of food restriction

ADULTHOOD UNDERNUTRITION

The following is a summary of the clinical experience of the medical staff of the Hospital de Enfermedades de la Nutricion of Mexico City [18–5]

Compensated Stage —Short stature will be an external manifestation of this stage only if the patient was undernourished during infancy Weight below the average in which both a decrease in subcutaneous fat and muscular underdevelopment are involved is the only obvious external sign The chemical composition of the blood and urine the white and red blood cells and other laboratory tests show no deviations from normal during this stage

Adaptation to decreased food intake is so great that people are able to carry on during this period and even to do heavy physical work when daily obligations force them to do so If there is no need for physical exertion they will do as little as possible This is one of the fundamental causes of the slow progress and the low economical yield per capita of the under nourished populations of the world There is no improvement of living conditions and there is only a drive to satisfy some of the more elemental forms of pleasure sexual activity and alcoholism As spermatogenesis and ovogenesis are not affected at this stage, the number of pregnancies increases This condition aggravates the woman s undernutrition The number of still born and of abortions increases and if the child is born he

is of smaller size and weight and is less resistant to infection If the mother has enough milk, breast feeding will permit some improvement in the child's nutrition, at the expense of the mother's health

The undernourished family can survive under these conditions for long periods of time, masking a very unstable equilibrium ready to break in the presence of any stress If chronic alcoholism develops, the economic capacity of the individual decreases and the family budget becomes smaller Such factors make it more difficult for the family to obtain enough food The unstable family situation is made worse The emotional disturbance of the lazy, alcoholic, sexually hyperactive, irresponsible and frustrated man increases He is thrown more and more into alcoholism and sexual excesses inside and outside the family The economic problem increases, working capacity decreases and anorexia becomes worse

Frequent pregnancies aggravate the condition of the women and can precipitate the severe form of malnutrition Usually, an intercurrent disease, even a mild one breaks the unstable equilibrium and throws the patient into the uncompensated stage of malnutrition

Uncompensated Stage — *Universal Signs* — The most conspicuous sign is weight reduction It is proportional to the imbalance between caloric intake and body requirements but can be modified by a great tendency to water retention This retention is not so important in adults as it is in children, but it always is present and clinical edema frequently is apparent The retained water is diffusely distributed and the retention is due more to a general dilution process than to hypoalbuminemia Associated mechanical factors will tend to localize water in particular places, *e g*, ascitis in cirrhosis of the liver, in the legs if varices are present, in the face in nephrotic patients, pleural effusion in congestive heart failure, etc Hyponatremia and acidosis are present only in the extreme forms

Circumstantial Signs —These are directly related to the food restriction and are present to a variable degree depending on the causes and mechanism of production of the severe stage The most important are the following

Skin manifestations —Skin pigmentation of the melanotic type is one of the most important external manifestations of undernutrition It generally has a diffuse distribution but tends to be more accentuated on the exposed portions of the body face, hands and feet It usually is described as pellagrous or pellagroid

A second type of pigmentation is the localized form It is present only on limited areas of the body surface, but has no special localization It usually appears as points, lines or plaques Sometimes it has the appearance of a reticulum

Another skin manifestation of undernutrition is due to vascular changes, *e g*, erythema on the dorsa of the hands and feet Cyanosis may be present Telangectases are observed during undernutrition but they are not associated with increased estrogen secretion Ecchymoses and purpuric pigmented dermatitis also are observed

The skin becomes dry, brittle and squamous, giving the impression of ichthyosis When edema is present the skin surface is smooth and brilliant, as frequently observed on the hands and feet

The skin appendages show marked changes The hair becomes scanty

and gray or red The amount of body hair, particularly the axillary and chest hair, decreases markedly and frequently disappears Nails become brittle and the oral mucosa and the tongue look reddish There is atrophy of the lingual papillae Sometimes mucosal pigmentations can be observed similar to those found in Addison s disease

Digestive Manifestations —Diarrhea is the most frequent of the digestive, disturbances of undernourished adults Glossitis stomatitis gingivitis anorexia, abdominal distention achlorhydria and decreased intestinal enzymes are other very frequent manifestations of poor nutrition The x ray reveals the peculiar picture of fragmentation snow flakes, dilatation and strictures of the small bowel These are not specific changes but frequently are observed in malnourished people during the severe stage of the disease

Eighty per cent of undernourished patients will have signs of liver involvement, particularly hepatomegaly The liver is soft and diffusely enlarged Liver function tests show a moderate to marked decrease in serum albumin and some increase in serum gammaglobulin Bromosulfalein retention when present is of moderate degree Liver biopsy shows fatty infiltration

Laennec s cirrhosis is not a consequence of undernutrition alone but it does occur when chronic undernutrition is associated with chronic alcoholism The presence of only one of these factors apparently is not capable of inducing the portal type of liver fibrosis

Hematologic Manifestations —Anemia is present in all undernourished individuals during the uncompensated stage of the disease It is of variable type as shown in Table 139

TABLE 139

TYPE OF ANEMIA OBSERVED ON UNDERNOURISHED INDIVIDUALS
(70 CASES)

Macrocytic anemia	57 %
Normocytic normochromic anemias	24 %
Hypochromic anemia	19 %

Macrocytic anemia is more common in males Hypochromic and normocytic normochromic anemias are more frequent in females Achlorhydria is a frequent accompaniment of the condition more so in hypochromic anemias than in other forms The severity of the anemia usually is of moderate degree

Neurologic Manifestations —Polyneuritis is the most conspicuous and frequent of all neurological manifestations Not frequently described but usually present in some degree are manifestations of involvement of the posterior and the posterolateral columns Higher functions of the central nervous system will be affected in severe cases of undernutrition Some evidences of CNS involvement are in fact present during the compensated stage such as laziness and lack of ambition If undernutrition becomes worse patients become drowsy and a state of unconsciousness ev[illegible] The severe forms show a severe attack on all cerebral activities [illegible]

fested by the dementia of pellagra, the Wernicke syndrome, and other forms of encephalopathy

Endocrine Manifestations.—Sexual function is markedly decreased Males show a picture of hypogonadism testicular atrophy, lack of axillary and scanty pubic hair Loss of libido and impotence are general Testicular biopsy reveals decreased size of the tubules, hypospermatogenesis and testicular fibrosis 17 ketosteroids are at a very low level There is a low excretion of urinary FSH, indicating the pituitary origin of the condition

Menstrual disorders are frequent Amenorrhea is present in 50 per cent of young women No increased menstrual bleeding has been observed There is mammary atrophy and absent or scanty pubic hair The vaginal smear and the endometrial biopsy are atrophic, and there is a low excretion of urinary FSH in young women Almost half of postmenopausal women show increased urinary FSH excretion, even when severe degrees of undernutrition is present This finding indicates that the pituitary of malnourished women is able to produce gonadotrophic hormones in large amounts when the ovary no longer is able to produce sex hormones

The adrenal gland is small The clinical picture has many of the symptoms described in adrenal insufficiency, but they can not be ascribed entirely to an insufficient gland Urinary 17 ketosteroid excretion is very low, urinary 17 hydroxycorticoids are low, but their concentration in the blood remains normal Patients showing edema or localized water retention have increased aldosterone and antidiuretic hormone excretion The response to ACTH administration is present but somewhat decreased because of adrenal atrophy The undernourished patient has a decreased ability to respond to stress because of this atrophic gland, but he still is able to resist aggression This adrenal reserve is demonstrated also by the response to insulin administration Undernourished individuals do not develop severe hypoglycemia as do addisonian patients

One of the fundamental facts about undernutrition is the low basal metabolic rate, however studies of thyroid function do not show any important decrease in thyroid activity blood protein bound iodine and radioactive iodine uptake are normal Thyroid histology shows a marked decrease in the height of the thyroid epithelium This finding indicates that the gland has some degree of hypoactivity, in spite of which the body cells are probably receiving enough thyroid hormone since there are no clinical signs of myxedema The thyroid hypoactivity (what little there is) responds to thyrotrophic hormone administration, suggesting that the condition has a pituitary origin

The overall clinical picture of the endocrine changes is similar to that of organic panhypopituitarism The two conditions are compared in Table 140

Associated Signs.—These are the result of a secondary disease or condition which usually precipitates the onset of the uncompensated form of undernutrition fever in infectious diseases, hyperglycemia, glucosuria or ketonuria in diabetes, increased basal metabolism, tremor hot and wet skin, muscular atrophy in hyperthyroidism, moon face, buffalo-type obesity muscular wasting in the Cushing syndrome, skin infiltration, low-pitched voice and dry skin in myxedema, steatorrhea in the malabsorption

syndrome, associated with abnormal xylose or radioactive iodinated triolein and oleic acid absorption from the intestines ascitis and severe liver damage in liver cirrhosis, tumor growth in malignant diseases etc

Recovery Stage—Clinical improvement begins as soon as effective treatment of the superimposed diseases is instituted Nitrogen balance quickly becomes positive

TABLE 140—DIFFERENTIAL DIAGNOSIS BETWEEN ORGANIC PANHYPOPITUITARISM AND ENDOCRINE HYPOACTIVITY DUE TO UNDERNUTRITION

Signs	*Organic*	*Nutritional*
Enlarged Sella turcica	Present sometimes	Not Present
Menstruation	Amenorrhea (100%)	Amenorrhea (50%)
Vaginal smear	Atrophic	Atrophic
Endometrial biopsy	Atrophic	Atrophic
F S H Urinary Excretion		
Female Premenopausal	Low	Low
Female Postmenopausal	Low	*High* (50%)
Male	Low	Low
Testicular atrophy	*Present*	Present
Urinary 17 ketosteroids (mgs 24 hs)	Low	Low
Urinary 17OH corticoids	Low	Low
Plasma 17OH corticoids	Low	Normal
A C T H Response	Delayed Positive	Delayed Positive
Aldosterone excretion	Present	Increased if edema is present
Basal Metabolic Rate	Low	Low
Protein Bound Iodine	Low	*Normal*
Radioactive Iodine Uptake	Low	*Normal*

Diarrhea Stops—*The weight of the patient* decreases during the first weeks due to water excretion and then increases Appetite increases slowly but steadily until it becomes normal and there is steady improvement in all the clinical manifestations Skin lesions desquamate until a new and clean skin appears Tongue ulcers clear up Mental and neurological signs decrease slowly Anemia and hypoalbuminemia improve Liver function tests improve and normalization is obtained by the fourth to the tenth week of treatment This is followed by the disappearance of the fatty infiltration of the liver

Sex activity returns to normal The first manifestation is a marked increase in urinary FSH excretion This is followed by estrogen production in the female and later by the presence of ovulatory cycles Males show a constant increase in 17 ketosteroids excretion and, between the fourth and tenth week, large amounts of estrogens appear intermittently in the urine They precede the appearance of gynecomastia The marked increase in estrogen excretion is not preceded by alterations in liver function but by a marked increase in FSH excretion This finding suggests that gynecomastia is due to excessive estrogen secretion secondary to excessive FSH stimulation of the testicles

Adrenal activity recovers as demonstrated by increased 17 ketosteroids and 17 hydroxycorticoids in the urine Electrolyte changes revert to

normal, thyroid activity normalizes during the recovery stage, as the basal metabolism increases At the end of three months the patient has completely recovered from all the signs of undernutrition, demonstrating this to be a reversible disease

ETIOLOGY

Undernutrition is the result of a discrepancy between food intake and body energy requirements[26] When this discrepancy is due to widespread economic and social conditions, the endemic type of undernutrition results[2] This type has been described in almost every nation Lack of technical knowledge of the production, conservation, transportation and preparation of food, illiteracy large families, poorly developed natural resources, and poverty are the responsible factors The inadequate food production is at present becoming worse due to the rapidly increasing birth rate and declining death rate

Besides community conditions, there are many individual situations to consider, *e g*, chronic alcoholism, disease, a poor sense of family responsibility, indolence and ignorance decrease the individual's desire and ability to protect and improve his nutrition and that of his family For these reasons, there are still many countries with rich natural resources and underpopulated areas in which undernutrition is frequent

Anorexia, a common cause of insufficient food intake, frequently is a manifestation of organic disease, and such should be looked for when anorexia exists If there is no evidence of an organic disease, the possibility of a mental type of anorexia must be considered Both children and adults ry frequently eat inadequately because of emotional disturbances Some rms of psychosis can produce a severe condition known as anorexia ervosa

Undernutrition also appears when there are increased energy require nents not compensated for by an increased food intake This may occur with excessive physical exertion, during traumatic shock, in the presence of metabolic diseases like hyperthyroidism and diabetes, or in febrile diseases Body protein consumption is manifested by muscular wasting and a rapid weight loss particularly in a previously well nourished person Under such conditions, the biochemical and clinical manifestations of undernutrition become apparent, even in people weighing more than the expected weight for age and height

MECHANISM

With the insufficient food intake there is a poor supply of the energetic and plastic materials required for anabolism Decreased cellular activity then results If the supply of energy and essential materials is still less than these lowered requirements, mobilization of endogenous fats and proteins then takes place to make up the deficit Because of this increase in protein catabolism, it has been thought that a possible explanation for certain symptoms observed during undernutrition is an insufficient synthesis of some specific proteins This possibility has been mentioned repeatedly

to explain the decreased pituitary activity in undernutrition,[8] however, as mentioned previously the two types of pituitary hypoactivity, organic and secondary to undernutrition, are not exactly the same (Table 140)

Experimental data prove that the pituitary is able to synthesize FSH, LH and ACTH at a normal rate in undernourished animals[9] Rinaldini and Pearse demonstrated that undernourished anestrus rats have greater than normal stores of pituitary FSH[4] We have recently demonstrated that undernourished rats accumulate large amounts of gonadotropins in the pituitary gland after castration, at the same rate as "ad libitum" fed castrated controls[8] The presence of large amounts of FSH in the urine of postmenopausal women during severe undernutrition proves also that this hormone usually the most severely reduced during starvation is secreted to a high extent if the ovaries are atrophic The bulk of evidence suggests then, that the pituitary can synthesize hormones during undernutrition but is not able to liberate them into the general circulation The presence of a functioning target gland seems to be the factor that directly inhibits pituitary function This fact can be explained only by the existence of a specific factor (hormone) circulating in the blood in such a concentration as to inhibit pituitary hormone release No satisfactory theory has yet been offered to explain the simultaneous presence of pituitary hypoactivity, glandular atrophy absence of peripheral effects of hormones and high blood hormone concentration capable of suppressing pituitary function

The clinical picture during the recovery stage is a manifestation of the normalization of all organic functions While all the body functions are becoming normal some of them are excessively stimulated The manifestations of excessive hormone stimulation have been attributed erroneously to insufficient hormone inactivation by the liver With the exception of secondary hyperaldosteronism no hyperhormonal syndromes are observed during the uncompensated stage of undernutrition They are present only during the recovery stage At this stage liver function improves quickly and is almost normal by the time the hyperhormonal effects develop Therefore, a different explanation for this phenomenon has to be offered

Hyperestrogenism is the hyperhormonal condition most frequently mentioned as occurring in undernutrition Our studies prove that the high estrogen excretion is never observed during the uncompensated stage of undernutrition, but is a constant finding in males and young females during the recovery stage and is always preceded by a marked increase in urinary excretion of the follicle stimulating hormone (FSH)[4] The high estrogen excretion stimulates mammary enlargement and suppresses pituitary FSH release This in turn decreases estrogen excretion and the pituitary gland is again able to liberate FSH Estrogen then reappears and stimulates still more mammary development This process repeats until a new normal relation between FSH and estrogen secretion is established In the course of this oscillation similar to a pendulum like movement some other activities become exaggerated due to the same mechanism These phenomena should not be attributed to liver insufficiency but should be considered as manifestations of a normal process of recovery

DIAGNOSIS

Undernutrition should be the diagnosis on any patient who is losing weight or who is underweight It is important to bear in mind that isolated deficiencies are not usually observed in anorexic patients or in the under developed and poorly nourished areas of the world Even in the presence of the clinical picture of a specific deficiency polyneuritis, pellagra, scurvy, rickets etc an underlying state of general undernutrition should be looked for

A precise diagnosis of the clinical stage of the disease should be established since each has a different prognostic and therapeutic meaning During the Compensated Stage, the condition is diagnosed if the analysis of the diet shows that it is below the accepted standards Undernutrition is also recognized if a child is not growing satisfactorily or his development is delayed Underweight is the fundamental clinical manifestation of undernutrition in adult patients If a patient is in the process of losing weight, he should be considered as an undernourished individual, whether or not his weight is normal

If a diagnosis of undernutrition has been established, the next step will consist of the identification of the primary cause of an inadequate food intake Beside social factors, organic disease and emotional upsets are the most frequent causes

The severity of the uncompensated stage should be determined in order to make a more accurate prognosis Three different degrees are observed in children First-degree-undernutrition is characterized by a weight ranging between 76 and 90 per cent of the theoretically correct weight for the child's age In second-degree-undernutrition the weight is between 61 and 75 per cent of the expected weight If the weight is below this range the child is classified as having a third-degree undernutrition

Severity is classified in adults according to the presence or absence of associated external manifestations of undernutrition Where there is only a decrease in weight and a history of a deficient diet, a patient is considered to have first-degree-undernutrition If there are slight to moderate skin or mucosal manifestations intermittent diarrhea or abnormalities in the liver function tests, or neurological manifestations, the patient is considered to have second-degree-undernutrition Third-degree is diagnosed when at least one of the clinical manifestations becomes obviously severe, such as pellagra stomatitis diarrhea, hypogonadism etc The presence of the uncompensated form of the disease suggests the existence of an associated factor the nature of which should be precisely determined

When weight gain and normal rate of growth return the Recovery Stage has set in Gynecomastia, in the adult male, estrogen activity in the young female, improvement of liver function tests also are indicative of recovery The appearance of ascites hepatomegaly, tetany or of hypertrichosis in a child also are evidences of improvement

Primary endocrinopathies must be distinguished from secondary endocrine hypoactivity due to undernutrition Male or female hypogonadism due to a primary gonadal disease is associated with increased urinary FSH

excretion If hypogonadism is due to organic pituitary failure it is associated with panhypopituitarism

Differentiation between undernutrition and chronic adrenal insufficiency is sometimes difficult In both cases there is loss of weight asthenia nausea and vomiting, diarrhea, anorexia skin and mucosal pigmentations, low urinary 17 ketosteroids and 17 hydroxycorticoids, and a negative water load test The response to ACTH administration is the only way to obtain positive evidence of adrenal destruction in the addisonian patient in contrast to a persistent but somewhat atrophied adrenal in undernutrition

PROGNOSIS

During the Compensated Stage prognosis depends on the severity of the etiological factor Manifestations of undernutrition are easy to reverse completely if food intake or increased energy requirements are normalized The only remaining sequela will be a short stature in children depending on the period of time during which growth was decreased or abolished During the uncompensated stage of the disease and when undernutrition is of great severity (second or third degree) the presence of a precipitating factor should always be suspected and treated Prognosis depends on the on the nature, severity and duration of the associated disease

The most important prognostic aid in second and third degree under nutrition in children is the presence or absence of electrolyte imbalance If present almost half of the children will die during the first 24 to 48 hours after hospital admission If there are no electrolyte changes, mortality decreases to 15 per cent [13]

Children and adults can effect a complete recovery from the uncompensated stage of undernutrition Mortality due directly to malnutrition is rare in adults Old people with prolonged undernutrition may die due to an intercurrent infection usually of the respiratory system Liver cirrhosis developing as a consequence of alcoholism and undernutrition, may cause *a liver insufficiency to persist as evidenced by abnormal liver function* tests, and associated portal hypertension of variable degrees Ascites if present during the acute stage will improve and usually disappear after the administration of a proper diet to the cirrhotic patient

TREATMENT

It is dangerous to force feed severely undernourished individuals After World War II the incapacity of the undernourished to metabolize large amounts of food during the uncompensated stages of starvation was observed Prisoners died suddenly when fed large meals soon after liberation from concentration camps

Children and adult patients should be offered a soft well balanced diet They should be permitted to eat as much or as little as they want As soon as the appetite increases and they are able to finish the portions served the amount of food can be increased until a full diet can be completely eaten This is usually observed after 4 to 7 weeks of treatment It is not convenient nor necessary as a rule to add extra vitamins amino acids or

proteins to the diet to initiate recovery Treatment should be individualized Sometimes the administration of these factors will retard improvement and produce some dangerous imbalances Gillman has reported a hastening of the onset of death after the addition of excessive quantities of food supplements to acutely malnourished infants with nutritional edema and intensely fatty livers[31] Androgens or other anabolic agents are of no use Acid base equilibrium should be restored as quickly as possible, dehydration and potassium deficiency should be corrected Calcium should be provided if tetany appears

General aseptic measures in regard to the skin, mouth, rectum eyes, ears and nose should be taken for the patients during the first few days of treatment Temperature changes or contact with patients suffering from contagious disease should be avoided

The precipitating factor responsible for the uncompensated stage and other complicating conditions should be diagnosed and treated, as early as possible In the presence of emotional factors responsible for the anorexia, psychotherapy and a better understanding of the environmental condition will help to normalize children's development The presence of the clinical picture of recovery does not require any treatment with the exception of calcium administration in tetany Treatment should be continued until appetite is normal the patient is gaining weight and the intercurrent disease has been cured

Treatment of the endemic form of human undernutrition is far beyond the scope of physicians alone and is related more to the solving of the great problem of human poverty

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Chapter 31

Nutrition in Diseases of the Nervous System and in the Psychiatric Patient

By Douglas Gordon Campbell

No other organ of the human body is so involved with all aspects of nutrition as the nervous system. Not only does the nervous system govern the seeking and preparation of nutrients in response to various hungers but it regulates their consumption and digestion, absorption, processing, transportation, and their eventual utilization by every cell of the body. Moreover like any other tissue of the body, the nervous system has its own basic nutritional requirements. If these are not provided by the very cells, organs, and systems it governs, reversible or irreversible damage to its own structure and function will ensue. Such impairment of neuropsychic and neurophysiologic functions establishes vicious circles which further disturb the metabolic activities of supporting tissues.

METABOLIC NEEDS OF THE NERVOUS SYSTEM

The governing functions of the nervous system which regulate all internal and external activities of the organism are the consequence of the extreme degree of specialization of nerve tissue for integration. Since specialization in biological systems necessitates increased dependency on the supportive functioning of less differentiated tissues, the nutriture of the human nervous system (which is about 25 per cent of the total metabolic activities of the body) is completely dependent not only upon the availability *of crude nutrients in the diet but also their digestion and absorption* by the gastrointestinal tract, their chemical transformation by other tissues, and their transportation by the blood-vascular system to the blood brain barrier for transfusion into the interstitial fluids of the brain.[1]

Current knowledge of brain metabolism is comparatively meager. The trophic unit of nerve tissue—the neuron—whether central or peripheral in location is ectodermal in origin but intimately dependent upon glial cells deriving from both ectodermal and mesodermal sources. A delicate pia-glial membrane—the blood-brain barrier—also originating from the same embryonic tissues acts as a semi permeable membrane between capillary blood and the interstitial fluids of the brain. The analysis of the functions of these cellular elements and their interrelations poses the most taxing problems in neurophysiology and biochemistry. *In vitro* experimentation must be interpreted with great caution. *In vivo* findings may be conditioned by unrecognized factors deriving from heredity, development, pre-existing diseases, and, in the human, by psychological conflicts of which the patient

himself is usually not aware We know that the nervous system is predominantly dependent upon blood sugar and oxygen[2] Deficiencies of either lead to a wide spectrum of clinical syndromes While chemical mechanisms for energy release and transformations of nutrients have been elucidated by combinations of the Embden-Meyerhof glycolysis and the Krebs citric acid cycle it is not known precisely which phases take place in neurons themselves and which in their supporting tissues Impressive as the dependency of brain tissue upon adequate supply and metabolism of glucose may be the anabolism and catabolism of proteins and lipids must also be important The variations in Nissl substance, the growth and regeneration of axiscylinders and myelin sheaths attest active and essential proteo-lipid metabolism requiring nitrogenous and fatty materials as also do the labile enzyme systems upon which cellular metabolism depends Certain vitamins[3] especially those of the B complex which are essential to carbohydrate metabolism must not only be in adequate supply from the diet but require the production of their co enzymes Minerals, particularly iron sodium and potassium are required by nerve tissue for its respiratory functions and to maintain the electrolyte balance of its fluid media Until further research clarifies the obscurities of intermediate metabolism of nerve tissue itself the only useful clinical approach toward maintaining or restoring the healthy nutriture of the brain is to apply our more advanced knowledge of the conditions governing the metabolic functions of those tissues which process and supply brain nutrients

CONDITIONING FACTORS

Conditioning factors are secondary causes of malnutriture[4] and since they may be operative despite an adequate food intake their recognition in neuropsychiatric conditions is very important The mere prescription of a well balanced diet together with supplements by oral or parenteral routes may be ineffective if conditions impairing assimilation are not alleviated

Psychosocial Factors—Within wide limits man chooses or creates his own nutritional environments both internal and external Because the human nervous system is unique in its ability to make and store forms of representation—meaningful symbols—which govern conditional responses it is peculiarly susceptible to its own past experience and to communications from other sources This is strikingly evident in human nutritional behavior everything connected with sustenance is symbolic and fraught with meaning For the human infant each feeding experience every foodstuff is linked at subcortical levels of integration with reactions of pleasure or pain depending upon the adequacy of the total nutritive experience Since the baby is fed by a nursing mother or her surrogate the nursing experience becomes a social experience and the whole process involving satisfaction or frustration security or insecurity love or hate may be represented symbolically by some part of the total situation An item of food its temperature texture and taste its adequacy to meet the immediate metabolic needs of the child the bodily characteristics such as warmth and odor of the nurse the physical surroundings etc to mention but a few of

the many stimuli impinging on the baby's nervous system as it is being fed, may, especially when repeated, condition its subsequent metabolic reactions Hunger, originating from the metabolic needs of various tissues, may be negatively conditioned or "inhibited" by fear, hate, and the real or imaginary deprivation of personal attention and love to produce such morbid inhibited states as marasmus in infants and anorexia nervosa in adults Or it may be deviated into voracious or capricious forms of appetite resulting in obesity and other types of malnutrition, not to mention a wide range of psychosomatic gastrointestinal disorders The psychiatric study of cases of malnutrition due to improper choice and quantity of food almost invariably reveals their source in emotional disturbances connected with the feeding of infants and children

Not only are attitudes toward foods and their ingestion conditioned by idiosyncratic experiences but also by the collective representations of society, as in racial, national, or religious nutritional habits As a matter of fact, such collective representations, indigenous to a culture and expressed in such forms as folk lore (*e g*, "meat is bad for the kidneys"), sacred and secular sanctions (*e g*, "meat arouses the animal passions"), and familial tradition have a profound but insidious effect upon man's choice and consumption of foodstuffs In all societies certain foods have meanings of weakness or strength, masculinity or femininity, inferiority or superiority, reward, punishment, and prestige, etc, with little regard for their actual nutritive values Since everything connected with foods and feeding is of psychosocial importance and therefore influences the production storage marketing, preparation, and serving of foodstuffs, dietary inadequacy may also be a conditioned or secondary cause of malnutrition By such mechanisms, largely unconscious in operation, *the human nervous system determines its own nutriture*

Certain neuropsychiatric disorders have a more specific effect upon dietary intake The feeding disturbances of *infancy and childhood* are frequently the expressions of depression due to deprivation of love, as in marasmus It has been repeatedly demonstrated that bottle-fed infants should be nursed in contact with the body of the food donor and that visual, auditory, and tactile relationships with people should accompany the feeding of all children so that the fundamental relationship of nutritive and social activities will be properly established Other feeding disturbances in the forms of specific cravings or aversions and disorders of ingestion such as dysphagia or regurgitation, are due to conditional reactions produced by the association of strong emotions with feeding activities Thus voraciousness or anorexia may represent the indulgence or repudiation of sexual cravings, the acceptance or rejection of social relationships, love or hate Anxiety originating from the insecurities of childhood and reactivated by the social stresses of *adolescence, maturity, and old age* manifests itself in various psychoneurotic and psychotic syndromes in which nutritional disturbances may be prominent Anorexia nervosa and obesity are only extreme examples of psychologically conditioned malnutrition Food fadism a common source of deficiency states, is usually the symbolic expression of sexual and aggressive drives and defenses against them Bizarre methods of oral ingestion and disturbances of deglutition,

periodic fasting, negativistic refusal to eat or drink occur in psychoneurotic states, such as hysteria and obsessive compulsive neurosis and in the major psychoses In all these conditions foods and feeding have acquired meanings which sometimes can only be revealed by the painstaking methods of psychoanalysis before the patient can be freed from their harmful conditioning effect upon his nutrition

Neurophysiological Factors —Certain neurological diseases interfere directly with the neuromuscular mechanisms of ingestion Some of these diseases are degenerative in origin, others infectious, and still others are due to specific deficiency states Neurohumoral disturbances of the pituitary adrenal axis may profoundly disturb nutrition by producing such extreme conditions as pituitary cachexia acromegaly or gigantism, thyroid and adrenocortical syndromes Pathological conditions affecting the diencephelon and autonomic nervous system may not only produce disturbances of the appetite and the exocrine and endocrine glands concerned with the digestion, absorption and chemical transformations of nutrients, but disrupt transportation by the gut and vascular system Neurophysiological disturbances of the nutritive apparatus of the body may be secondary products of many neuropathological conditions and it should not be overlooked that the intrinsic metabolism of the nervous system is particularly vulnerable to certain medical and surgical procedures employed in neurology and psychiatry

Other Conditioning Factors —*Ingestion* —Anorexia may occur from the shock of surgical procedures pain from any cause cardiovascular and hepatic condtions, infectious diseases toxic infectious states from prolonged starvation, and deficiencies of thiamine and other members of the B complex Food allergies may lead to the voluntary or medically directed avoidance of essential nutrients The prescription of restricted diets for gastrointestinal cardiovascular and metabolic diseases often results in malnutrition which deprives the nervous system of blood sugar and other essential nutrients Therapeutic starvation of one organ damages the organism as a whole vicious circles of starvation are easily established malnutrition may be iatrogenic

Increased Nutritive Requirements —Nutritive requirements are increased in any prolonged strenuous physical activity, in the delirium of intoxications and fevers and the agitated phases of certain psychoses Hyper tension of smooth and striated muscles is excessive in anxiety states and many neurological diseases The use of thyroid, corticoids, insulin parenteral dextrose and high carbohydrate diets will increase requirements for certain nutrients

Absorption —The absorption of nutrients from the gastro-intestinal system may be interfered with by factors producing achlorhydria, deficient gastric and intestinal enzymes, biliary disease, hypermotility, or reduction of the absorbing surfaces Deficient absorption may also be produced by vitamin deficiency and by the therapeutic employment of acid-neutralizing medicaments liquid petrolatum, cathartics and by drugs which irritate the mucosa or interfere with peristalsis Surgical operations involving resection and short circuiting of the gastrointestinal tract may

seriously interfere with absorption so that hypoglycemic and hypoproteinemic conditions arise

Hepatic Functions —The utilization of nutrients required by the nervous system depends upon the integration of the mechanisms of intermediate metabolism occurring in glandular and other tissues While no one phase of these interlinked biochemical processes may be considered more essential than another, it is nevertheless evident that the liver plays a major role not only in the processing of brain nutrients but in their storage This means that any causes of hepatic dysfunction may interfere with the metabolism of the nervous system The liver is primarily dependent upon the gastrointestinal tract for supplies, and it is therefore subject to the same conditioning factors that regulate appetite, ingestion, digestion, and absorption

The detoxifying functions of the liver have long been known the biochemical mechanisms responsible for conjugation, oxidation, reduction, methylation, and acetylation require adequate dietary and at times increased supplies of essential nutrients as well as intact neurohumoral apparatus Malnutriture of the liver makes it particularly vulnerable to endogenous and exogenous toxins Some drugs used in neurological and psychiatric practice produce their effects by interfering with the enzyme systems of cellular respiration and cognate metabolic processes in nerve cells or their supporting tissues The promiscuous use of barbiturates and other sedatives, of stimulants such as amphetamine, or antispasmodics and analeptics, etc , in neuropsychiatric disorders not only impedes normal metabolism but may precipitate nutritional crises, especially if the detoxifying functions of the liver are subnormal The treatment of intercurrent infections of the nervous system or peripheral tissues by sulfonamides and antibiotics may also impair normal metabolic processes upon which both liver and nervous system are dependent

THE ASSESSMENT OF THE NUTRITIONAL STATUS IN NEUROLOGICAL AND PSYCHIATRIC DISEASES

The importance of nutritional therapy in most diseases of the nervous system and in psychiatric patients would be better recognized if physicians would train themselves to evaluate the nutritional status of their patients Many neurological diseases involve permanent structural damage to nervous tissues which not only interferes with normal bodily activities but may, in addition, require strenuous compensatory efforts, thereby compounding conditions of stress Psychoses of long standing usually suffer from both primary and secondary deficiencies of food intake not to mention disorders of intermediate metabolism Many acute psychoses, especially those following severe bodily stress such as the post partum reactions, show mild to severe malnutrition with reciprocal disturbances of the hepato-cerebral and neuro glandular axes The subjective complaints of mental and physical fatigue so frequently present in psychoneurotic patients often have a partial foundation in long-standing defects of ingestion or assimilation Preventive psychiatry should also concern itself with the nutritional

habits of children and adults, to remove malnutrition as a factor in the production of maladjustment

The Nutritional History —Of prime importance in the detection of actual or potential deficiency states is the nutritional history This should commence with data from the family history Some estimate of the available food supplies, racial national, and family customs, and the actual eating habits during childhood may provide clues not only indicative of childhood dietary deficiencies but about those early interpersonal relationships which condition lifelong attitudes toward the choice and amount of food consumed From such data concerning the social setting of childhood feeding experiences the astute physician is able to make valuable inferences about the probability of a patient's cooperation in therapy

The chronology of growth and development and of past illnesses should be looked upon as points on the curve or graph of a patient s nutritional history Adventitious episodes of starvation due to socially imposed stresses such as war or adverse economic conditions are additional points on this curve Further data of great importance may be gathered from evaluation of the patient s character structure as revealed by the record of behavior problems neurotic or psychotic illnesses, and the patient's current attitudes toward himself his illness and his medical attendants The more complete the nutritional history the more light will be shed on the factors of familial and individual malnutrition as possible etiologic factors of nervous and mental diseases Stress from any cause at any time in the life history may affect the metabolism of specific tissues and thereby condition the nutriture of others so that their adaptability to any subsequent stress may be permanently impaired The clinical patterns of alarm, resistance and exhaustion of the general adaptation syndrome are in part predetermined by the nutriture of organs prior to assault

Data on the feeding habits of childhood are frequently difficult to obtain even with the aid of relatives, so that they must often remain inferential Current patterns of food ingestion are best gathered by having the patient or responsible observers record every detail of at least one week s intake of nutrients The nutritionist may then estimate the relative importance of deficencies or excesses of essential nutrients for the particular pathological conditions found For clinical expediency briefer techniques of dietary analysis consisting of check lists and rough quantifications, are available in the standard texts

Clinical Examination —The physician should be alert to the clinical signs and symptoms of malnutrition In the course of the neurological examination itself, specific malnutriture of nervous tissues may be revealed by disorders of sensation, abnormalities of muscle power and coordination by tremors, and by disturbances of superficial and deep reflexes Special attention should be directed toward any signs or symptoms of hepatic dysfunction since liver pathology accompanying the neuropathies of chronic alcoholism and other exogenous toxins is in all probability only an extreme example of a spectrum of hepatic disturbances to be found in many neurological and psychiatric diseases

There is no limit to the range and ingenuity of laboratory investigations [4] but they should never be a substitute for careful interviewing and the clinical examination

GENERAL PRINCIPLES OF DIETOTHERAPY IN NEUROLOGY AND PSYCHIATRY

The Role of the Nutritionist—Most important in the prescription and administration of diets is an awareness on the part of the nutritionist of the personal relationship between him and the patient. From the point of view of the patient, any person who gives, modifies, or withholds foods is in a controlling position and will be associated, unconsciously, with those *personalities on whom he was dependent in childhood*. Consequently, attitudes of trust or distrust, passive submission or defiant rebellion may be induced in the patient and condition not only the ingestion of prescribed nutrients but their assimilation as well. The success or failure of the most ideally constructed diet is often determined by emotional reactions of the *patient toward the nutritionist or food donor*. *Doctors, nurses, servants,* or relatives concerned with the modification and serving of the patient's diet consciously or unconsciously communicate their own attitudes toward foodstuffs and toward the patient. As physicians or nutritionists it is incumbent upon them to be aware of the psychosocial factors conditioning *human nutrition and to select their representatives in the actual prepara*tion and serving of foodstuffs with care. Ill-cooked, unattractively served meals may be made even more repugnant to a patient when presented for consumption by food donors who are hurried, disinterested, authoritarian, untidy in appearance, or otherwise hostile in their attitudes. It is the nutritionist's responsibility to supervise the administration of the diet he has prescribed by the selection of proper assistants, inspection of the food served, and, if possible, by visiting the patient at mealtimes.

The nutritionist should employ his technical knowledge of the metabolic requirements of a disease process within the setting of cultural background, economic status, and individual psychology of his patient. This means that foodstuffs must be symbolically acceptable and any serious *modification of a patient's food habits dealt with* with tact and reassurance, compromise and compensation. A skillful use of *motivation will overcome* many objections to dietary change, since patients are not really interested in the nutritional values of foods as such, but in what diet may accomplish for them in terms of strength and appearance, sexual adequacy, prestige, and health. Stereotyped diets should provide some range of choice of *individual nutrients, printed or mimeographed lists* should be avoided, diets should be tailored to the individual, offered, not ordered. Nutritionists should use both scientific and intuitive understanding to circumvent negative attitudes, for any modification of food consumption, no matter how justifiable nutritionally, tampers with the sources of emotional life and is comparable to attempts to alter religion or politics. Dietotherapy can be a form of psychotherapy using non-verbal symbolism to affect the deepest levels of the mental apparatus. This is not exclusively a problem of frank psychiatric disorders, negative *reactions to the nutritionist* who tampers with his diet may be covert or frankly overt in any patient. All illnesses involve the personality to some extent and produce varying degrees of regression in which immature forms of interpersonal relationship

may reappear. After all, infantile behavior occurs surprisingly frequently in healthy adults at the family table, in restaurants and in food shops, so that it is understandable that the stress of ill health may unmask or intensify such attitudes. If the nutritionist will take the time to learn something of his patient's early nutritional experiences by inquiring about nursing, weaning, food preferences and aversions and previous illnesses, together with sufficient data about early family relationships which might affect basic attitudes of trust and security in the presence of authority figures, he may make some valuable inferences about his potential role in his patient's life. With the exception of certain patients who are compulsively dependent, obedient, and submissive, any authoritarian, autocratic or rigid attitudes in the prescription and administration of diets should be avoided. Again with certain exceptions the nutritionist should assume an attitude conforming to the maternal stereotype of our times, in which features of personal interest and warmth, generosity and permissiveness, good humor and encouragement are combined to win the patient's cooperation. A diet should be prescribed for a person rather than a disease.

NUTRITION IN PSYCHIATRY

Psychiatric disorders range from the behavior problems of childhood to the chronically deteriorated states of senile psychosis. All involve disturbances of interpersonal relationship in the pathogenesis of which malnutrition may play primary or secondary roles. With the exception of those reaction types where hypo- or hyperalimentation is conspicuous, scant attention has been paid to the nutriture of the majority of psychiatric patients. This is partly due to the fact that contemporary clinical psychiatry is predominantly psychological in its orientations and leaves to other specialists the investigation and therapy of somatic dysfunction. It is also partly due to the covert or subclinical nature of malnutrition in the general population from which most psychiatric cases are somatically indistinguishable. Yet careful methods of investigation directed toward an appraisal of nutritional status reveal malnutrition in many psychiatric patients. This should not be surprising in view of the well-known effect of anxiety upon appetite and assimilation. In some cases acute or chronic malnutrition appears to precipitate psychiatric illness but in the majority it contributes to the intensity or chronicity of neurosis or psychosis in a secondary way by becoming part of a vicious circle. Regardless of its causal position in psychiatric syndromes, nutritional therapy usually shortens the duration of ill health.

According to current psychiatric knowledge, many reaction types have their immediate causation in some stress producing situation in the patient's life which reactivates basic anxiety and the defenses against it that were acquired in infancy or childhood. This means that inadequacies of character structure arising from the blend of inborn constitution and biological drives modified by the restraints imposed by the demands of social adaptation, make a given individual vulnerable to specific types and degrees of life stress. Anxiety, no matter how subjective and psychological it may appear to be, invariably involves physiological mechanisms. The neuro-

glandular and neuromuscular excitations not only produce somatic signs and symptoms, the awareness of which causes further augmentation of the original anxiety, thereby establishing vicious circles, but necessarily disturb nutritional processes in varying degrees. The pre existing nutriture of a patient, itself the product of constitution and previous stress, will be a determinant along with character structure and other factors, of the acuteness, chronicity, and responsiveness to therapy in psychiatric illness. It is very important, therefore, to make a careful evaluation of the nutritional status in all psychiatric patients and to correct any long standing or recently acquired malnutrition.

General Principles of Nutritional Therapy in Psychiatry.—Since in many psychiatric illnesses chronic anxious tension is present, there has usually been prolonged malnutrition. Acute episodes may therefore produce very serious nutritional breaks leading to chronic disability. If the nutriture of the patient has not been undermined by long-standing inadequacies of ingestion and assimilation, the nutritional disturbance accompanying acute illness, even though intense, can usually be quickly repaired. In all psychiatric cases involving acute or chronic malnutrition, it should be assumed that deficiencies of essential nutrients are multiple, that anxiety, while it may conspicuously affect ingestion quantitatively or qualitatively, invariably affects assimilation, that nutritive requirements are increased due to greater energy expenditure, and that drugs and therapeutic measures such as electroconvulsion and insulin hypoglycemia disturb intermediate stages of metabolism, in particular those of the liver.

Guided by these assumptions, subject to variation from case to case, the dietary needs of all patients in a state of anxious tension are much greater than the normal requirements of health. The more tense the patient and the longer the duration of the illness, the greater will be the nutritive requirements.

Infancy and Childhood.—The feeding disturbances of infancy and childhood are usually conditioned by emotional factors originating from some acute or chronic disruption of the child's familial relationships. The most severe form is *marasmus*, which has been shown to result occasionally from emotionally catastrophic situations in which physical separation of the infant from adequate maternal contact has occurred.[5] Feelings of isolation and abandonment may supervene rapidly and produce an acute stage of alarm in which the precarious metabolic balance may be shattered despite adequate food supplies. As the metabolic mechanisms of infancy become more stable during childhood, the physiological consequences of such conditioned malnutrition become less acute, but nonetheless harmful for growth and development. If dietary supplies are adequate, disturabnces of ingestion and assimilation usually reflect tensions in the family relationships (bio-physical causes being eliminated) so that therapy must be directed at the psycho-social situation. There are, however, many conduct disorders of childhood which may be produced or aggravated by inadequate food supplies. In the nursing period quantitative and qualitative insufficiencies of breast milk or bottle formulas may produce prolonged crying and restlessness which may provoke impatience in immature or misguided parents, attendants, etc., to compound the biological sources of insecurity

with anxiety due to "disciplinary" measures of isolation rejection, or even physical punishment. Under such conditions we have all the ingredients for the establishment of neurotic patterns of adaptation. Even when great patience is shown the experimentation with different formulas prolongs biological insecurity and often establishes a sort of mythology about a child's uniqueness, need for special handling, and, by implication, its lifelong obligations to its worried parents.

Inanition from any cause frequently produces over-intense attitudes toward feeding situations. These may be expressed as generalized voraciousness (which could arouse competitiveness and rejection in the social milieu) or as refusal to eat and anorexia—a type of defense against repeated frustration that has secondary gains in terms of parental and medical concern for the sickening child. Irritability, temper tantrums, altered states of consciousness, delinquent behavior in the form of stealing food or its symbolic equivalents (*e g* money) and the protean manifestations of inevitable guilt-anxiety that derive from such behavior and further complicate the behavioral disturbance may be associated with hypoglycemia or deficiencies of other nutrients resulting from primary or secondary food deficiency. The nutritionally oriented physician, aware of the increased metabolic requirements during periods of rapid growth and in states of anxious tension, should not assume an exclusively psychogenic explanation until he has carefully investigated food intake and assimilation. In many cases the prescription of a generous diet, catering as far as possible to the child's tastes, may produce quick improvement. Even in profoundly disturbed children where malnutrition is secondary to psychogenic causes, liberal dietary supplies not only correct malnutriture but express affection and reassurance in the non-verbal imagery of a child's emotional life. In aiding a child to achieve normal development and strength through the provision of adequate supplies and the correction of any faulty assimilation the physician alleviates a fundamental source of inferiority feelings and social isolation.

When prescribing corrective diets for both disturbed and emotionally healthy children it should be borne in mind that both the child and its family or guardians have to be considered. As far as the child is concerned restrictions of favorite food items should be minimized and special cravings indulged where possible; authoritarian attitudes may nullify the purpose of the dietary changes, a generally permissive attitude will produce better cooperation. Changes in quality, quantity, and timing of children's feedings may clash with the nutritional beliefs and customs of parents and other adults directly responsible for child care. This will require tactful explanation and compromise. Usual cravings or aversions, food allergies, and other idiosyncrasies affecting intake may require specialized psychotherapeutic efforts since in childhood, both foodstuffs and routines of eating are readily associated with people and social situations through strong feelings of affection and fear. The labile autonomic and neuroglandular apparatus of childhood easily disrupts the synchrony of digestion, absorption and utilization when stimulated by negative emotions. The disapproval or prohibition of candies and the ubiquitous soft drinks or other foods may arouse feelings of resentment, guilt, inferiority, etc., and cause more

emotional harm than nutritional improvement unless a skillful use of motivation is employed In this connection the physician may need to use a therapeutic group situation in order to employ the powerful sanctions of communal feeding patterns The responsibilities of families and institutions in providing happy, tension-free feeding situations for disturbed as well as healthy children are matters of public health The actual dietary needs of children will not be discussed in this chapter, since they are covered in Chapter 35, save to point out that the nutritive requirements of children who are anxiously tense or who have suffered inanition from any other cause, are greatly increased, especially so when such disturbances occur during periods of rapid growth Complete proteins and a wide spectrum of vitamins and minerals should be provided in amounts well above the basic requirements

Adolescence—In adolescence, emotional disorders begin to assume adult forms of neurosis, psychosis, and social deviancy Rapid growth, sexual maturation, heavier sports, physical labor, and greater educational pressures combine to produce increased expenditures of energy and augmented nutritional needs Adaptation to adult standards normally produces anxious tension, which may become excessive if disturbed interpesonal relationships occur because of delinquency, neurosis, or psychosis Nutritional breaks are common and protean in their manifestations The precarious equilibrium of chronic malnutrition that may have been relatively symptom-free during childhood may suddenly collapse under physical or psychological stress to produce acute systemic disease or personality disorders Poor performance in educational activities in school may be caused by malnutrition[6] The grades of failing students have been improved by prescribing more adequate diets The nutritional management of maladjustments in adolescence and early maturity is simpler than in childhood because appetite is greater (with the exception of depressed cases), motivations more accessible to stimulation, and parental interference from nutritional prejudices less The caloric intake should be considerably higher than that of a normal adult of comparable size, with much greater emphasis on complete proteins for their tissue-building properties Severe malnutrition will need the type of management employed in adult cases but with provision for the added requirements of growth

ADULT PSYCHIATRIC ILLNESS

In certain acute and chronic psychiatric illnesses disturbances of ingestion and assimilation are so pronounced as to endanger survival They require emergency measures of nutritional support, such as parenteral or nasal feedings, and richly supplemented oral feedings Hypoalimentation, with anorexia and inanition, occurs frequently in the psychoneuroses, the addictions, and the psychoses Hyperalimentation, usually producing obesity, may also occur in these reaction types, but when the excessive intake is assayed it is often found to be deficient in many essential nutrients although high in calories Severe malnutrition, no matter what its origin, not only impedes psychotherapy because it is a threat to biological survival,

but it consolidates a vicious circle by forging a somatogenic link in the chain of causes of mental disturbance

Anorexia may be primary or secondary, acute or chronic and occur at any age When it is primary and predominant, it is labeled *anorexia nervosa,* a psychoneurotic condition usually but not exclusively found in young, unmarried women

Dietotherapy of anorexia nervosa will depend upon the degree of starvation and the resistance of the patient Many such patients will either make no effort to consume even liquid nourishment or they will complain of nausea distention, and inability to swallow, and even secretly regurgitate what they have compliantly swallowed In such cases tube feeding by a nasal catheter of polyethylene plastic should not be postponed Depending upon the degree of gastrointestinal disturbance the content quantity, and timing of the feedings must be variable Severe cases are comparable to the extremely debilitated cases found in German and Japanese concentration camps who had suffered such extensive disturbances of gastrointestinal and hepatic functions that they could only assimilate small quantities of fat-free milk Accordingly the slow hourly or half-hourly injection into the nasal catheter of 50 to 100 cc of fresh or reconstituted skim milk to which a liquid multivitamin formula together with small amounts of pepsin or essence of caroid pancreatic enzymes bile salts and trace minerals have been added is the safest procedure in severe inanition Aspiration of stomach contents before each feeding is often helpful at first Each such injection should be followed by a rinse of 1 to 2 cc of decinormal hydrochloric acid further diluted with water Parenteral 5 per cent glucose-saline solution, to which may be added a sterile, high potency polyvalent, water soluble vitamin solution should be given slowly intravenously is required to combat dehydration and acidosis The oversupply of oral nutrient mixtures, especially hydrolyzed proteins and fat emulsions may cause nausea emesis, distention diarrhea aggravating the existing disturbance The composition of the nasal feedings prepared in a blender should be strengthened very cautiously by the addition of dextrose skim milk solids and soy bean oil When dehydration and acidosis are corrected varieties of protein fat and carbohydrate should be built into the solution in small but increasing amounts up to the point of tolerance Powdered brewer s yeast is a good source of protein and important micronutrients but may require increased amounts of digestive supplements to facilitate digestion Powdered whole liver or other animal proteins are excellent if available in powdered forms It is probably wise to avoid raw eggs in early stages Hydrolyzed proteins or pure amino acids are indicated only if pancreatic disease is a conditioning factor their high cost may be avoided if adequate amounts of digestive supplements are supplied with natural complete proteins Dextrose may be replaced by cane sugar or syrups Emulsified fat solutions are now available Many days and weeks may elapse before the optimum ingestion of a balanced mixture containing 3 500 to 4 000 calories daily is attained As a rule it is unwise to encourage eating and drinking at early stages since this requires additional expenditures of energy and the patient may not be emotionally ready to accept such a socially responsive relationship The introduction of self feeding, partic-

ularly of solids, should be treated as a weaning process, that is to say, with correct timing, tact, patience, and appeal to appetite. Perhaps no other psychiatric illness requires such a combination of nutritional knowledge and psychological insight as anorexia nervosa.

Secondary Anorexia and Inanition.—Anorexia may be a chronic or episodic accompaniment of emotional disorders wherein other reactions are primary. Thus it is usually secondary to narcotic and alcohol addiction, the prolonged use of drugs such as the barbiturates and amphetamine, and it is commonly found in toxic-infectious reactions, senile and arteriosclerotic psychoses, and the deteriorated phases of chronic "functional" psychoses. Self-imposed fasting in obsessional neurotics, religious fanatics, food faddists, and as a result of delusions in schizophrenic states will also produce a secondary anorexia. It is most commonly found, however, in the milder psychoneurotic and psychosomatic illnesses seen in general practice. The more chronic and inconspicuous the anorexia, the more insidiously damaging will be its effects, for chronic malnutrition not only lowers bodily resistance to physiobiological stressors but to psycho-social stress as well. Some acute psychiatric illnesses would neither occur nor become chronic, and would be more amenable to psychotherapy if malnutriture due to chronic anorexia were prevented. A careful nutritional history may be necessary for its recognition.

The treatment of chronic anorexia is not only dietetic but psychiatric, since the original and underlying causes are usually to be found in neurotic or psychotic evaluations about foods, feeding, and health. In many cases psychosocial factors must be discovered and corrected first, and this may require deep psychotherapy before adequate cooperation in a program of nutritional rehabilitation can be obtained. Many persons, however, lose their anxiety about food consumption when the physician is kindly, reassuring, and takes the time and personal interest to correct acquired misconceptions and, by appeal to overt or covert motivations, replace them with nutritional information designed to meet individual needs.

The dietetic management of chronic anorexia and subnutrition consists in well-designed, "tailored-to-measure" meals and the generous use of appropriate supplements. Scanty breakfasts, characteristic of the morning depression of harassed 'normal' as well as neurotic people, should be replaced with a major meal containing one-third of the daily protein quota together with high amounts of energy foods. Lunch should also be high in protein and energy foods—quite the equivalent of the large breakfast. Supper should be simple and relatively light since energy needs are usually decreased and appetite for breakfast will be greater if a large evening "dinner" is not consumed. The protein quotas in anorexic states should be gradually increased to levels of at least 125 to 150 gm. daily, depending upon clinical findings since chronic malnutrition is usually associated with inefficient utilization and wastage. Energy foods will also need to be increased proportionately to achieve caloric levels well above N.R.C. recommendations. Vitamins and minerals should be in ample supply for reasons previously discussed.

Intermediate nourishment in the office, school, or home is often obligatory to meet the nutritional needs of poor eaters. Liquids have several

advantages over solid foods as sources of extra nourishment They may be attractively prepared to include a variety of essential nutrients, they are easily consumed and have a particular psychological appeal to many psycho neurotic patients Milk should be the base of such mixtures unless contra-indicated because of 'allergy' or psychological reasons

It will be found that as protein consumption improves the frequently pathological craving for carbohydrates will subside without the necessity of prohibiting them good foods should displace poor ones In general it is wise to give anorexic and other chronically malnourished patients food lists and means providing multiple choices, not only to supply a wide range of nutrients but to imply permissiveness generosity and freedom of choice Many psychoneurotic individuals are food faddists, and it is well to avoid great emphasis on any one item or mode of diet that might foster their neurotic preoccupations Foodstuffs can easily become the ammunition and mealtimes the battle ground of a neurotic struggle with authority

Psychosomatic Illnesses —Many psychosomatic illnesses will not clear up until malnutrition is corrected, yet such patients, well known for their oversensitive, ambitious and usually proud characters, will usually offer many rationalizations against needful changes in their diet In psychosomatic illnesses, improved nutrition facilitates psychotherapy just as reciprocally, psychotherapy facilitates the aims of the nutritionist

Obesity —Obesity is generally accepted today as being predominantly psychogenic in origin and psychotherapy of every type is being employed with variable effectiveness [7] (See Chapter 30)

Addictions to narcotizing drugs and to alcohol (itself a narcotic) involve problems of chronic inanition and the antimetabolic effects on cellular enzyme systems of exogenous toxins Gastrointestinal pancreatic and hepatic functions, together with brain respiration may be disturbed to the point of irreversible pathology The neurotic adaptation to any psycho-social stress precipitating the addiction is compounded by the effects of the particular drug consumed The possible presence of genetotrophic factors as suggested by Williams [7] is worthy of serious consideration when investigating the medical and dietary history character structure and the influence of cultural factors No matter what the constitutional or psycho-social causes may be any prolonged addiction will reveal malnutrition usually of severe degree While this is obvious in the acute episodes to prolonged use of opium derivatives cocaine marijuana barbiturates and alcohol, it may be masked by 'normal' or increased weight in some cases unless a careful examination is made The promiscuous use of barbiturates and other "mild" sedatives is one of the most common causes of malnutrition in psychiatric patients appetite is usually depressed and assimilation inhibited Therefore, the nutritional rehabilitation of these cases is as urgent as their psychotherapy The methods to be followed are those described above for anorexia and starvation but particular attention should be given to hepatic support by heavy supplementation of high protein high caloric diets

Alcoholism, because it is an addiction of endemic proportions and because alcohol is itself a source of energy requires special consideration Apart from psychosocial considerations alcohol is a 2 carbon carbohydrate

yielding 7 calories per cc, as such it is readily metabolized and displaces other energy-producing nutrients Although in small doses it stimulates appetite-secretions, in larger amounts it inhibits gastro intestinal functions, thereby interfering with the assimilation of other nutrients although itself quickly absorbed Chronic alcoholics rarely consume an adequate diet and indeed, there is suggestive evidence that many cases are the victims of genetotrophic or other causes of enzyme deficiencies impeding various phases of intermediate metabolism [8] Whatever the causes in a particular case most chronic alcoholics suffer from inanition

The dietotherapy of excessive drinking is of great importance both for prevention of further malnutrition and "cure" The prevention of damage from alcoholic beverages is primarily one of reduced consumption—a notoriously difficult psychosocial problem akin to obesity—and secondarily the intake of a high protein, high vitamin diet In practice it has been found that encouraging the consumption of a liberal high protein diet with ample vitamins frequently reduces the need to drink, at least it prevents progressive nutritional damage Psychotherapy and rehabilitation are facilitated by restoring a sense of physiological well being

Acute alcoholic states may require the withdrawal of alcohol intake if due to acute intoxication or the cautious administration of alcohol, parenterally if necessary, if the symptoms are aggravated by deprivation In either case dehydration, inanition, and shock will probably require the administration of parenteral fluids containing electrolytes, glucose, amino acids and polyvalent water-soluble vitamins until such time as gastro-intestinal functions are restored Ascorbic acid and sodium chloride[9] in large doses are helpful in some cases With recovery of the capacity to swallow and retain food, intermediate nourishment with an attractive milk formula should be encouraged Such preparations are usually very acceptable, for psychological reasons, to most alcoholics The use of insulin in small doses with parenteral glucose may be justifiable in some cases, but its general use is questionable and usually unnecessary with well-designed tube feedings and diets

The psychoses present widely varied nutritional problems The ingestion of food may be interfered with by distractibility, agitation, mania, negativism, depression, and stupor, assimilation is frequently hindered by psychosomatic mechanisms or by chronic inanition Acute malnutrition is usually superimposed upon a chronic marginal state and may rapidly produce an extreme stage of exhaustion with imminent death unless emergency procedures are employed Chronic malnutrition is the standard finding in young asthenic schizophrenics, prolonged depressions, and most deteriorated "back ward" cases The emotional turbulence of the sometimes lengthy pre-psychotic state may insidiously damage nutriture so that resistance to stress of various kinds is decreased and relatively minor stresses may precipitate acute psychotic reactions When a psychotic pattern becomes well organized, even without much deterioration, there is a tendency toward stabilization of nutrition at lower levels of intake and utilization but with lessened energy output, and deficiency syndromes develop which undoubtedly contribute to chronicity and deterioration The nutritional history of random samples of the psychotic population

warrants the assumption that conditioned malnutrition has existed for many years prior to psychotic breakdown in many cases There is a need for well organized nutritional surveys of our psychotic population to verify these clinical observations, but in the meantime physicians should obtain as detailed a dietary history as possible from relatives of their patients, and they should also examine their patients carefully for clinical signs of deficiency The feeding of psychotic patients, especially in state hospitals is frequently inadequate due to a combination of factors such as disinterest and resistance on the part of the patients, inadequate nutrients both poorly cooked and served, crowding and lack of supervision In some states the per capita allowance for the feeding of hospitalized psychotic patients is less than that provided for inmates of penal institutions Statistical averages that appear on the dietitian's and superintendent's desk by no means represent the actual consumption of individual patients, and what food is consumed may be incompletely assimilated because of conditioning factors In the 'total push therapy" of groups of chronic deteriorated patients, much of their improvement is due to increased consumption, to supplementation, and more attractive, monitored food service

Forced feeding is obligatory in psychotic patients who are resistant, in states of toxic exhaustion or comatose This is accomplished by means of nasal catheterization as described for anorexia As a rule, however, the psychotic inability to eat is of fairly recent origin and assimilation has has not been severely damaged, so that richer and larger amounts of liquid feedings can be employed It must be borne in mind that psychotic patients are under acute stress and if they are agitated, their energy requirements are very much higher than normal

Convulsive therapy of any type must be regarded as the artificial imposition of a life endangering stress with the aim of eliciting constructive processes of adaptation While there is probably less interference with metabolic mechanisms by electrical stimulation inhalations of carbon dioxide and prolonged narcosis by drugs than when insulin is employed to produce hypoglycemic coma, all such methods produce varying degrees of anoxia along with other effects on the metabolism of the nervous system Anoxia is, of course extremely hazardous to neurons of the central nervous system Hypoglycemia itself can reach irreversible levels and it imposes great strain on hepatic functions Details of insulin hypoglycemic therapy will not be discussed here but attention is called to the urgent need for large amounts of complete proteins and the water soluble vitamins in general nutritional management Between treatments the patient should receive a high caloric, high protein diet supplemented with vitamins and minerals of which sodium and potassium chloride are most important A yeast-milk preparation can make up for any deficiencies in the standard hospital diet or a patient s incapacity to consume sufficient solid foods Prolonged coma and other refractory reactions can usually be prevented by such nutritional measures, excessive weight gain following the long course of insulin therapy can be avoided

Recovery from any acute psychiatric illness should not justify the resumption of previous dietary habits The stress of acute or chronic mental illness has probably made alterations in the complex chain of

interrelated metabolic processes and will require an improved dietary regimen for a long time Relapses, all too frequent in neurosis and psychosis when inadequacies of character and physique are again exposed to life stresses, may be diminished in incidence and severity by improvement of the general nutriture

NUTRITIONAL MANAGEMENT OF DISEASES OF THE NERVOUS SYSTEM

Neurological diseases are no more or less "organic" than psychiatric disorders but their substrate of cellular pathology is predominantly microscopic and, *en masse*, may eventually become macroscopic consequently symptomatology is characterized by signs more referable to discrete anatomical structures than occur in psychiatric or so-called "functional" disorders However, microscopic changes of cell structure are invariably preceded by submicroscopic alterations involving disturbances of enzyme systems and the metabolism of macro- and micronutrients On the assumption that such submicroscopic disturbances both precede and accompany any microscopic cellular pathology, it may soon be possible to assign many neurological diseases to biochemical disturbances and to recognize the contributory effects of abnormal metabolism in others From the practical orientation of nutritional therapy it is useful to classify neurological diseases into those in which malnutrition arises from dietary deficiency or from disturbances of assimilation, transport and utilization, etc , and those due to other causes (*e g* , degeneration, infection, toxemia, trauma, etc) wherein malnutriture of the nervous system is secondary and contributory Both groups require dietotherapy and the correction of conditioning factors affecting the utilization of any nutrients

Regardless of etiology mild or severe degrees of malnutrition are often present in neurological diseases, especially when they are chronic This is scarcely surprising when the reciprocal relationships of the nervous system and peripheral organs are considered Most neurological diseases act as alarming life stresses to patients since they are apt to be physically incapacitating and, because of the great psychological values attached to nervous integrity, they are apt to produce considerable anxiety Their nutritional management, therefore, requires insight, tact, and reassurance on the part of the therapist in addition to his capacity to diagnose and manage any conditioning factors

Neurological Diseases in Which Malnutrition Is a Primary Factor —In this group are the so-called deficiency disorders such as beriberi, pellagra, Wernicke's encephalopathy, the Korsakow syndrome combined degeneration of the spinal cord, many neuropathies, and others

Dietotherapy —Replacement therapy, when known deficiencies exist, is often more effective in disorders of peripheral tissues (*e g* , scurvy and rickets) than in the neuropathies of malnutrition This is in part due to the limited capacity for regeneration characteristic of nervous tissue but conditioning factors such as gastro-intestinal disorder and hepatic dysfunction also play a role Therefore, the irreversibility of some nervous

lesions and their clinical effects should not discourage further search for and correction of metabolic disorders

Empirically the arrest or improvement of stubborn deficiency syndromes can often be attained by the scrupulous attention to any conditioning factors interfering with the intricate stream of metabolism together with a dietary regimen designed to supply all essential nutrients in easily assimilable forms and in amounts which according to a patient's tolerance should exceed the normal requirements of health Only a combination of nutritional science and shrewd clinical observation can determine the specific requirements of individual cases It is of great importance to take into account the often insidious and prolonged antimetabolic effects of many of the drugs used to treat neurological or concomitant diseases If they must be used their potential damage should be offset by larger supplies of those nutrients which support the detoxifying functions of the liver and compensate for the destruction inactivation or elimination of essential metabolic agents

Nutritional Encephalopathies —Several types of encephalopathy have been described as the consequences of malnutriture of the nervous system In symptomatology they may be mild or fulminating transient or chronic, early or late in their association with other neurological and systemic signs which establish the diagnosis of a neurological deficiency syndrome

The *encephalopathy of pellagra* in this country is usually insidious in onset mild with seasonal fluctuations the principal symptoms resembling anxious tension states neurasthenia or a mild depression and if a careful nutritional history is not taken or some of the characteristic systemic signs of pellagra are not present not recognized or only develop later this mild encephalopathy may be considered psychogenic and ineffectively treated (see Chapter 11)

Niacin deficiency[10] has been shown to be an essential causative factor in a group of stuporous and psychotic states where conditioned malnutrition due to alcoholism gastro-intestinal disease post surgical debilitation and cachexia from arteriosclerosis malignant disease poverty and senility exists The excessive hydration of seriously ill patients has been known to produce the syndrome [11] Pellagrous signs are not present but there may be polyneuritis scurvy and evidence of other deficiencies The patients are frequently old living alone on a grossly inadequate diet and any premonitory symptoms are frequently attributed to senility or arteriosclerotic encephalopathy Clouding of consciousness or actual coma grasping and sucking reflexes cogwheel rigidity and polyneuritis are usually present together with variable soft tissue signs such as stomatitis vaginitis and follicular keratinization indicative of other deficiencies The mental changes respond specifically to massive dosage of niacin or its amide Up to 1 000 mg daily in divided doses should be administered together with therapeutic amounts of the other known vitamins minerals and macronutrients This encephalopathy due to deficiency of niacin may contribute to the symptomatology of certain toxic psychoses where clouding of consciousness delirium exhaustion and evident malnutrition are present Such reactions may be precipitated by pregnancy lactation drug addiction or the stress of acute and chronic illness

Wernicke's encephalopathy[11] is a clinical entity more specifically related to thiamine deficiency It is characterized by the insidious onset, at any period of life, of depression, disorientation, loss of memory with a tendency to confabulate, unsystematized delusions and transient hallucinations, disturbances of vision, anorexia, and vomiting, etc, which progress to stupor and the appearance of a predominantly external type of ophthalmoplegia, generalized ataxia and usually polyneuritis It is most invariably associated with long-standing malnutrition due to alcoholism, prolonged dietary deficiency, the cachexia of malignancy, chronic gastrointestinal disorders, the toxemic states of pregnancy and renal or hepatic disease Lesions, predominantly in the diencephalon and midbrain, are primarily vascular with secondary parenchymal changes While thiamine deficiency is a prominent feature, it is obvious that there are associated insufficiencies of other B vitamins along with inadequate utilization of the macro-nutrients Polyvalent parenteral and oral vitamins featuring thiamine, niacin, and ascorbic acid in large amounts, together with dietary measures appropriate to the gastrointestinal tolerance and general nutritional state of the patient are indicated

Encephalopathies with less specific symptomatology may occur in connection with deficiencies of ascorbic acid, as sometimes seen in scurvy, or in association with endogenous and exogenous toxins Alcohol, opium and its derivatives, barbiturates and other popular sedatives used so promiscuously in medical practice will, in large dosage or prolonged administration, produce more or less specific encephalopathies which ordinarily disappear with the discontinuance of the drug[12] Cerebral symptoms due to drugs are undoubtedly aggravated by chronic malnutrition, that is deficiency states in which vitamin imbalances, insufficiency of electrolytes and other micro nutrients, anoxia, hypoproteinemia, hypoglycemia, and inadequacies of lipid metabolism occur Endogenous toxins, as in eclampsia, uremia, and acute hepatic disease, may also produce disturbances of brain metabolism The *Korsakow syndrome*, in which chronic encephalopathy and polyneuritis combine in varying proportions to produce mental and physical deficits with bizarre compensatory efforts characterized by confabulation and delusion, is a unique result of chronic malnutrition affecting a nervous system impaired by infection, intoxication, trauma, or circulatory deficiency Needless to say, conditioning factors must be ameliorated to permit nutritional rehabilitation While irreversible tissue damage has usually occurred, it is frequently surprising, in view of traditional clinical experience, how much recovery can be achieved by aggressive methods of nutritional therapy

Hence, the treatment of any encephalopathy wherein the nutritive supplies of the brain are curtailed or thrown out of balance will necessitate not only the removal or neutralization of the toxic agent by appropriate medical and pharmacological pr ... but the rapid correction of mal nutriture w ... ins, minera ... rous feeding

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asthenia, and progress to the signs and symptoms of a severe peripheral neuritis involving cranial nerves as well Neuropathy of autonomic nerves accounts for cardiac irregularities and gastrointestinal dysfunction and possibly also edema Encephalopathy, if it occurs tends to be of the Wernicke type with clouding of consciousness and ocular palsies Pellagrous and scorbutic signs and symptoms may complicate the clinical picture and attest the existence of multiple deficiencies Consequently the nutritional management of beriberi, while making the parenteral administration of massive doses of thiamine mandatory, requires proportionate amounts of the other water-soluble vitamins and balanced diets in forms and by routes appropriate to the patient s clinical condition

Polyneuritis u clinically and pathologically indistinguishable from the polyneuritis of beriberi, may occur as a prominent or subordinate manifestation of any illness interfering with the availability of cocarboxylase—the coenzyme of thiamine—for neural metabolism Starvation because many nutrients as well as carbohydrate and thiamine are more or less proportionately reduced, is less likely to be accompanied by polyneuritis and other nutritional neuropathies than illnesses which establish an imbalance of utilizable nutrients The increased demands of normal physiological stresses such as pregnancy and lactation the extremes of climate and the demands of physical labor may produce a relative deficit along with pathological conditions such as the increased metabolic demands of fever hyperthyroidism the antimetabolic effects of endogenous and exogenous toxins and increased elimination Treatment by thiamine alone, or even in multi vitamin preparations although effective in acute cases of recent origin is apt to be disappointing because polyneuritis when diagnosed frequently is chronic with irreversible nerve damage This illustrates the now established therapeutic experience that chronic lesions are much less responsive to replacement therapy than are mild or severe tissue reactions due to acute recent deficienceis [2]

Neurological Conditions in Which Nutritional Disturbance is Secondary, Contributory, or Concomitant —Neurological diseases in which heredity degenerative processes inborn errors of metabolism new growth cardiovascular disease trauma and infection play prominent etiological roles commonly show mild to severe signs and symptoms of malnutrition If a careful history reveals malnutrition during developmental phases or in periods of life-stress preceding the onset of the disease adaptation to any pathogenetic condition will be hampered [1] If malnutrition develops during the course of the disease itself adaptive processes will be further hampered Vicious circles are prone to develop the disease process and its therapy producing conditioned malnutrition which in turn impedes the regenerative needs and compensatory efforts of a damaged nervous system A very important contributory factor in such conditioned malnutrition is the augmentation of anxiety due to the patient s awareness of physical and mental impairment from nervous disorder

Degenerative Diseases —These diseases of the nervous system include a wide range of disorders in which degenerative changes of nerve tissue occur prematurely Some are hereditary or familial of unknown etiology and may be present at birth but more usually appear after a variable

period of apparent normal function. Other degenerative disorders are attributable to senescence, to arteriosclerosis and other vascular pathology, or to nutritional deficiency. Most degenerative diseases involve not only the dissolution of nerve tissue but the breakdown of muscle and other tissues as well. The spastic and flaccid paralysis of muscle not only produce nitrogen loss and a decreased reservoir of glycogen, but much anxious tension due to pain and disablement. Autonomic disturbances in certain of these diseases lead to anorexia, faulty assimilation, and hormonal disturbances. Sensory loss may expose the patient to trauma and infection, as in syringomyelia and multiple sclerosis. All these diseases interfere with the normal activities of the total organism, cause abnormal expenditures of energy, and therefore require carefully planned nutritional support.

Multiple sclerosis has received more nutritional attention than other degenerative disorders with the exception of the deficiency syndromes described above. Studies of blood proteins by Volk *et al.*,[13] reveal excessive nitrogen loss. The role of unsaturated fats versus hard fats has been studied extensively by Swank,[14] who recommended a special low fat diet containing 15 gm. of vegetable or fish oil. The protein intake is maintained at about 60 gm. daily and the balance of the caloric need is obtained from carbohydrates. The average caloric intake is set at about 1700 calories for a 130 lb. woman and at 1900 calories for a 145 lb. man. Patients are kept somewhat below (5 to 10%) the normal average weight. It is claimed that the diet reduces the frequency and exacerbation of the disease.

Enthusiastic claims for the improvement and arrest of multiple sclerosis (as well as muscular dystrophies and myasthenia gravis) by means of a high caloric diet composed of moderate amounts of fresh animal proteins including unpasteurized milk and its products, fertilized eggs, butter and oils, but not processed fats, and whole grains, preferably in germination, have been made by Evers.[15] Obviously the dietetic features of this regimen are comparable to the so called "natural" diets sponsored by food faddists in this country. The avoidance of allergenic foodstuffs and desensitization procedures in multiple sclerosis has not achieved the results expected and would only seem justifiable if definite allergic states are demonstrable.[16]

Cerebrovascular diseases require exacting attention to the underlying circulatory insufficiency and intensive nutritional support.

The *combined system disease of the cord* (sometimes affecting the brain and peripheral nerves) that accompanies pernicious anemia may be arrested by the use of parenteral vitamin B_1 (see Chapter 11).

The Myopathies.—*Progressive muscular atrophy* appears in several forms according to the age of onset, the musculature affected, and its association with pyramidal tract disease as in *amyotrophic lateral sclerosis*. The bulbar form is the most serious because of the progressive paralysis of the muscles of deglutition and respiration. In the later stages of all forms feeding, swallowing, and coughing becomes first a threat and then the usual cause of death. The muscular wasting, contractures, disablement, and interference with vital needs not only produce literal starvation but extreme anxiety which establishes a vicious circle. Consequently, intensive nutritional support should be instituted in the earliest phases of all myopathies, aiming

at possible arrest and prolongation of remissions, and the maintenance of morale

The *muscular dystrophies* are also of unknown etiology Van Meter[18] has claimed marked improvement by the supplementation of the diet with 3 teaspoonfuls daily of a proprietary casein hydrolysate mixture containing moderate amounts of the water- and oil soluble vitamins small amounts of iron peptonate and tribasic calcium phosphate together with 2 capsules daily containing 50 mcg B_{12} and 3 34 mg folic acid However these results lack confirmation

Convulsive Disorders —Hereditary and biogenetic disturbances have been hypothecated as the principal source of so called "idiopathic epilepsy" Mechanical pressure from wounds and tumors destruction and scarring from inflammation and vascular lesions cortical degeneration from any cause may produce epileptogenic foci or release phenomena While surgical and medical procedures may be very effective in the alleviation of convulsive phenomena due to tangible brain irritants pharmacotherapy is the mainstay in grand mal, petit mal pyknolepsy narcolepsy, and epiletpic equivalents (neuropsychic and autonomic phenomena), although it offers little else than suppression of neural excitations through interference with cellular enzyme systems

The nutritional therapy of the idiopathic epilepsies has been disappointing despite the earlier enthusiasm for the ketogenic and dehydrating diets While failures may with considerable justification be attributed to non cooperation of patients and their attendants when away from the disciplined facilities of an institution, such diets are difficult to prepare and rapidly become unpalatable in prolonged use Ketogenic diets are scarcely worth attempting except for investigational purposes in an institutional setting

In certain rare cases of convulsive manifestation in young children the administration of large doses of pyridoxine results in control of the seizures That pyridoxine deficiency is present in these patients can be demonstrated by the increased urinary excretion of xanthurenic acid following ingestion of tryptophane [19]

Mental Deficiency —Malnutrition is common in severe forms of mental deficiency with multiple physical handicaps The general principles of dietary treatment which were discussed in the section on debilitating neurological conditions should be applied to these patients The feeding of a large number of institutionalized severely defective children may be facilitated by the use of commercial preparations containing a combination of highly nutritious ingredients and blended in proportions to supply all nutrients including vitamins and minerals in a balanced diet The dried ingredients are mixed with water or with milk to make a stiff gruel heated and served In some rare form of mental deficiency metabolic alterations are present which in certain instances can be corrected by specially prepared diets Administration of the diet brings about correction of the metabolic alteration and not frequently improvement of the mental status Dietary control is effective in the following two diseases

1 *Galactosemia* is a congenital condition characterized biochemically by a deficiency of galacto-transferase an enzyme which is important in the

period of apparent normal function. Other degenerative disorders are attributable to senescence, to arteriosclerosis and other vascular pathology, or to nutritional deficiency. Most degenerative diseases involve not only the dissolution of nerve tissue but the breakdown of muscle and other tissues as well. The spastic and flaccid paralysis of muscle not only produce nitrogen loss and a decreased reservoir of glycogen, but much anxious tension due to pain and disablement. Autonomic disturbances in certain of these diseases lead to anorexia, faulty assimilation, and hormonal disturbances. Sensory loss may expose the patient to trauma and infection, as in syringomyelia and multiple sclerosis. All these diseases interfere with the normal activities of the total organism, cause abnormal expenditures of energy, and therefore require carefully planned nutritional support.

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Cerebrovascular diseases require exacting attention to the underlying circulatory insufficiency and intensive nutritional support.

The *combined system disease of the cord* (sometimes affecting the brain and peripheral nerves) that accompanies pernicious anemia may be arrested by the use of parenteral vitamin B_1 (see Chapter 11).

The Myopathies.—*Progressive muscular atrophy* appears in several forms according to the age of onset, the musculature affected, and its association with pyramidal tract disease as in *amyotrophic lateral sclerosis*. The bulbar form is the most serious because of the progressive paralysis of the muscles of deglutition and respiration. In the later stages of all forms feeding, swallowing and coughing becomes first a threat and then the usual cause of death. The muscular wasting, contractures, disablement, and interference with vital needs not only produce literal starvation but extreme anxiety which establishes a vicious circle. Consequently, intensive nutritional support should be instituted in the earliest phases of all myopathies, aiming

at possible arrest and prolongation of remissions, and the maintenance of morale

The *muscular dystrophies* are also of unknown etiology Van Meter[18] has claimed marked improvement by the supplementation of the diet with 3 teaspoonfuls daily of a proprietary casein hydrolysate mixture containing moderate amounts of the water- and oil soluble vitamins, small amounts of iron peptonate and tribasic calcium phosphate together with 2 capsules daily containing 50 mcg B_1 and 3 34 mg folic acid However, these results lack confirmation

Convulsive Disorders —Hereditary and biogenetic disturbances have been hypothecated as the principal source of so called idiopathic' epilepsy Mechanical pressure from wounds and tumors destruction and scarring from inflammation and vascular lesions cortical degeneration from any cause may produce epileptogenic foci or release phenomena While surgical and medical procedures may be very effective in the alleviation of convulsive phenomena due to tangible brain irritants pharmacotherapy is the mainstay in grand mal petit mal pyknolepsy narcolepsy, and epiletpic equivalents (neuropsychic and autonomic phenomena) although it offers little else than suppression of neural excitations through interference with cellular enzyme systems

The nutritional therapy of the "idiopathic epilepsies has been disappointing despite the earlier enthusiasm for the ketogenic and dehydrating diets While failures may with considerable justification be attributed to non cooperation of patients and their attendants when away from the disciplined facilities of an institution, such diets are difficult to prepare and rapidly become unpalatable in prolonged use Ketogenic diets are scarcely worth attempting except for investigational purposes in an institutional setting

In certain rare cases of convulsive manifestation in young children the administration of large doses of pyridoxine results in control of the seizures That pyridoxine deficiency is present in these patients can be demonstrated by the increased urinary excretion of xanthurenic acid following ingestion of tryptophane[19]

Mental Deficiency —Malnutrition is common in severe forms of mental deficiency with multiple physical handicaps The general principles of dietary treatment which were discussed in the section on debilitating neurological conditions should be applied to these patients The feeding of a large number of institutionalized severely defective children may be facilitated by the use of commercial preparations containing a combination of highly nutritious ingredients and blended in proportions to supply all nutrients including vitamins and minerals in a balanced diet The dried ingredients are mixed with water or with milk to make a stiff gruel, heated and served In some rare forms of mental deficiency metabolic alterations are present which in certain instances can be corrected by specially prepared diets Administration of the diet brings about correction of the metabolic alteration and not frequently improvement of the mental status Dietary control is effective in the following two diseases

1 *Galactosemia* is a congenital condition characterized biochemically by a deficiency of galacto transferase an enzyme which is important in the

metabolism of galactose An intermediate metabolite, galactose-1 phosphate accumulates in all tissues and is presumably toxic Impaired mental and physical growth, hepatomegaly and cataract are the main clinical manifestations Dietary treatment consisting of a diet adequate in all respects but lacking in galactose (and lactose), results in normal physical and mental development of the child, provided the diet is instituted early enough before irreversible changes have taken place

2 *Phenylketonuria* is a condition characterized by a deficiency in the metabolism of phenylalanine resulting in the urinary excretion of high amounts of phenylpyruvic acid, phenylalanine and other phenyl compounds Mental deficiency is usually present and it is thought that the presence of some abnormal phenyl compound inhibits normal mental development

Administration of an adequate diet low in phenylalanine results in the disappearance of the characteristic biochemical features of the disease and, when the treatment is instituted during the first months of life, in normal mental development[20] Several low phenylalanine preparations are commercially available, among which are Ketonil (Merck), a casein hydrolysate to which carbohydrate and fat must be added, and Lofenalac (Mead Johnson & Co), a balanced low phenylalanine food containing protein, fat and carbohydrates with vitamins and minerals It is supplied in powder form and is easily mixed with water for use as an infant formula or as beverage for children

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Chapter 32

Nutrition in the Care of the Surgical Patient

By I S Ravdin and Harold A Zintel

The importance of adequate nutrition in the surgical patient cannot be overemphasized The many physiologic derangements associated with nutritional deficiency produce distinct disadvantages to the patient and complicate surgical treatment Insofar as possible and practical it is the surgeon's duty to see that nutritional deficiencies are corrected preoperatively Prompt attention to nutritional problems will not only reduce the patient's discomfort and increase his sense of well being but will reduce surgical morbidity and mortality

There is reason to believe that when the dietary intake of a previously healthy individual is markedly reduced for as little as ten to twelve days vitamin deficiencies may occur which can reduce his physical fitness and his resistance to disease and interfere with normal wound healing Weight loss below the normal is an obvious but very important indication of malnutrition Malnutrition may be the result of (1) inability to ingest food because of pain, vomiting or obstruction, (2) inability to digest and assimilate food, or (3) continued bleeding as from carcinoma of the gastro-intestinal tract It is well recognized that, except for vitamin K deficiency the clinically recognizable vitamin deficiencies are rare It is not sufficiently appreciated, however that a subclinical vitamin deficiency may cause profound disturbances of the physiological processes of the body

On the day of a surgical operation and for several days thereafter nutrition is frequently inadequate Following an illness of several hours and an appendectomy, weight loss is frequently 5 pounds in four or five days Following a gastric resection or abdominal perineal resection, weight loss may be as much as 20 to 25 pounds, in addition to any preoperative weight loss that may have occurred Hypoproteinemia predisposes to poor wound healing or disruption of wounds delayed healing of fractures anemia, failure of gastro-intestinal stomas to function, embarrassment of pulmonary and cardiac function, and reduced resistance to infection

Protein —The most common deficiency is that of protein Such a deficiency is especially serious in surgical patients because proteins are the building blocks for the repair of tissues In addition they are necessary for the transportation of lipids in the body and for the maintenance of normal blood volume, serum protein level and total circulating blood cell mass Finally they provide amino acids for the formation of antigens hormones antibodies and enzymes A daily intake of 60 to 120 gm of protein is adequate for an active, healthy adult provided his caloric intake is adequate In the presence of infection trauma and even extensive immobility of parts or all of the body there is rapid breakdown of protein within the body as

indicated by increased nitrogen and potassium excretion in the urine In the burned patient and in patients with other types of trauma with extensive skin loss, there is in addition to the catabolic breakdown of protein, a considerable loss of protein directly from the surface of wounds, and also a decreased utilization of ingested protein All of these factors lead to the rapid production of severe hypoproteinemia It is well established that in previously healthy adults with an inadequate total caloric intake, a normal protein intake of 60 to 120 gm may be inadequate, because protein may be deaminized and transformed into carbohydrate to help provide energy for the body Nutritional edema, which occurs frequently in individuals living in areas devastated by war, may be abolished by increasing only the caloric intake in the form of carbohydrates provided the daily intake of protein was and remains adequate Protein is not stored in the body as

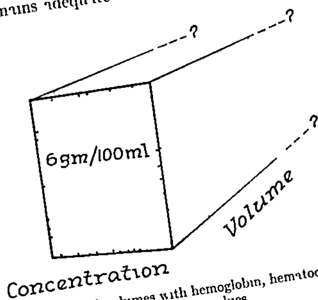


Fig 63 —Blood volumes with hemoglobin, hematocrit and serum protein values

fats and carbohydrates are An inadequate caloric intake and a zero protein intake for more than a few days may produce a serious reduction of the total amount of protein of the body cells, serum, and intercellular fluid

Recognition of Protein Deficiencies —The most practical way of recognizing protein deficiency is by weight loss A weight loss of 10 pounds or more in an adult, occurring over a period of a few days or weeks, is an excellent indication of deficiency The best laboratory method of demonstrating a protein deficiency is measurement of the blood volume Associated with the reduced blood volume a reduced total circulating serum protein and a reduced total circulating red blood cell mass are found Furthermore, serious reductions of the previously mentioned values may occur before any significant reduction is observed in the hematocrit, hemoglobin or serum protein values (See Figs 63, and 64) Indeed a decreased serum protein level is usually a very late manifestation of hypoproteinemia Initially, there is a reduction of total circulating serum protein and total circulating red cell mass Under the usual circumstances

the blood does not become more dilute The blood volume decreases and the effective volume of the cardiovascular tree is reduced Thus, the concentration of serum protein, hemoglobin and red blood cells (hematocrit) per unit of blood initially is preserved When this compensating mechanism (contraction of the vascular tree) has reached its limit, then the hemoglobin, hematocrit, and serum protein values fall for the first time below normal levels Observations during acute hemorrhage in man and in animals would indicate that from 25 to 30 per cent of the normal blood volume is lost before reduction of hemoglobin hematocrit and serum protein values

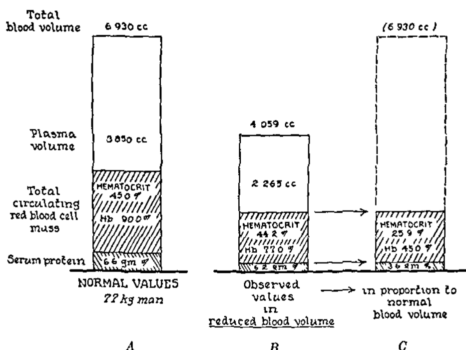


FIG 64 – Inadequacy of serum protein value without other data

Column *A* represents the normal blood volume, hematocrit hemoglobin and serum protein values for a 77 kg man

Column *B* represents the values as demonstrated in a 77 kg patient treated by the authors The relative concentration of red blood cells hemoglobin and serum protein are within normal limits in spite of the fact that the total circulating red blood cell mass and the total circulating amount of protein are greatly reduced If the observed blood volume of this patient was increased from the determined figure of 4 0◡9 cc to the normal value of 6 930 cc by the addition of only fluid then the hematocrit would be 2◡5 9 per cent the hemoglobin 45 per cent and the serum protein 3 6 gm per cent as shown in Column *C*

The patient had a duodenal ulcer and received 1500 cc of whole blood before operation This is approximately half of the amount of his blood volume deficit of 2 871 cc When the abdomen was opened and before any exploration of the peritoneal cavity was attempted the anesthetist announced that the patient was in shock The pulse was above 100 the systolic blood pressure was below 100 mm of Hg the skin of the face was pale and the skin of the extremities was cold This example demonstrates how easily shock can be precipitated in the hypovolemic hypoproteinemic individual Restoration of the blood volume to normal values preoperatively would have considerably reduced the risk of operation Actually the operative procedure was discontinued until an adeqauto amount of blood had been administered

are obvious The serum protein value is a very poor early indication of protein deficiency because it is significantly reduced only after a serious deficit has occurred (Fig 64) The patient who has a definite protein deficiency and is to have an extensive surgical operation should receive preoperative nutritional or replacement therapy even though the serum protein, hematocrit, and hemoglobin levels may not be decreased

Protein Deficiency and Shock —The reduction of blood volume, decreased circulating serum protein (with or without a decrease in serum protein level), and decreased total circulating red blood cell volume predispose the surgical patient to shock and hypoxia Champ Lyons[1] has described this "syndrome" as a chronic shock Actually, this is a very poor term, for the patient is certainly not in "shock" The patient's condition is such that he is more apt to develop shock than a normal individual The most common and perhaps the only causes of early, traumatic shock are *hemorrhage*—the loss of whole blood or blood products either internally or externally—*hypoxia* or *anoxia*—of circulatory or respiratory origin—and *brain damage* It is, therefore obvious that the patient with reduced blood volume, reduced circulating serum protein level, and reduced red blood cell mass (and therefore, reduced total oxygen carrying capacity) would be most susceptible to the development of shock The patient with a protein deficiency may, therefore, develop shock on the operating table following a seemingly minor blood loss or moderate embarrassment of cardiac and/or respiratory function from either operation or anesthesia

Protein Deficiency and Wound Healing —In 1938, Thompson Ravdin and Frank showed that hypoproteinemia caused delay in wound healing and was also a major causative factor in wound dehiscence They showed that in hypoproteinemic dogs there was a marked delay in fibroblastic proliferation and a subsequent delay in wound healing Figure 65*C* shows complete healing at the end of two weeks in a control animal with a normal serum protein level Figure 65 *B* shows, under higher magnification, the degree of separation of muscle fibers by edema fluid in the experimental hypoproteinemic animal An adequate amount of building material in the form of protein results in good wound healing, whereas a deficiency of building material increases the possibility of wound disruption

Edema and Protein Deficiency —When the body protein stores are deficient and the serum protein level is lowered edema develops The osmotic pressure of the serum protein is only about 25 mm of mercury in excess of the protein content of interstitial, extracellular fluid This can be compared with some 5,000 to 6,000 mm of Hg for the osmotic pressure of the crystalloids The concentrations of the crystalloids within and without the vascular tree are equal or nearly equal, and their osmotic pressures counteract one another Therefore, the remaining effective osmotic pressure within the vascular system is equivalent to 25 mm, the osmotic pressure of the plasma protein In other words, the force which maintains fluid in, and drains fluid into, the vascular tree is equivalent to 25 mm The force which counteracts the osmotic pressure of the plasma protein is the blood pressure The blood pressure in the capillaries varies between 32 and 12 mm from the arterial to the venous side

When the serum protein level falls below 7 gm per cent, the force which

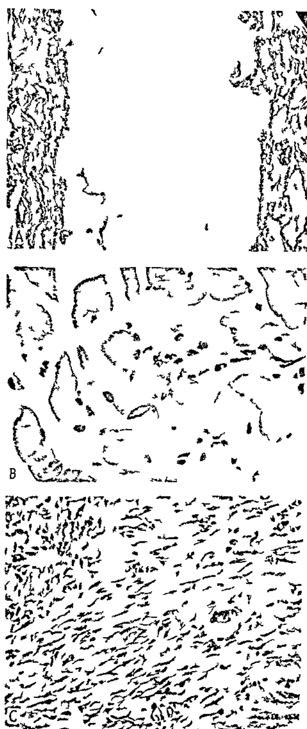


Fig 6ɔ —Wound healing in a hypoprote nem c dog 1 Complete d rupt on of ex perimental wound at the e d of two weeks *B* Mu cle fil ers widely separated with edema fluid *C* complete wound heal ng in a normal dog at tl e en l of two weeks

tends to retain fluids within and the force which attracts fluids back into the vascular tree is reduced and, therefore, fluid may collect in the interstitial spaces. The development of edema can be accelerated by the administration or the retention of excessive amounts of water and/or sodium. Considerable fluid may collect in these spaces before clinical edema develops, for edema is not grossly apparent until the weight of the affected part is increased by about 10 per cent with excess fluid. Excessive tissue fluid may embarrass the heart, the lungs, the liver, gastrointestinal tract and other organs. Accidental trauma and trauma by cutting and manipulation of tissues as in surgical procedures and the "trauma" of infection, cause serum proteins to escape from the capillary vessels and may produce varying degrees of localized edema.

Protein Deficiency and a Nonfunctioning Gastro-enterostomy.—Edema causes hypomotility and atony of the gastrointestinal tract. Mecray, Barden and Ravdin[3] have shown that hypoproteinemia produces a lengthening of gastric emptying time and a lengthening of the stomach-to-cecum time for a water-barium meal. Localized edema of the gastrointestinal tract may cause failure of a gastro-enterostomy to function. The edema of hypoproteinemia, the edema of trauma of operation, and possibly some edema associated with local infection may be sufficient to produce a complete mechanical obstruction in an otherwise perfectly formed stoma.

Protein Deficiency and Bone Healing.—Rhoads and Kasinskas[4] have shown that a deficiency of protein markedly affects bone healing. They have found that sometimes for as long as seventy-six days after the division of a bone in hypoproteinemic animals, there was little evidence of callus formation, whereas animals with normal serum protein showed good callus formation at the end of thirty-nine days. The cause of the delayed bone healing is not at once clear. Hypoproteinemia is known, however, to interfere with the fibroblastic repair that normally precedes callus formation. Concurrently, hypoproteinemia also causes a hypocalcemia, since approximately half of the serum calcium is bound to the serum protein.

Correction of Acute Protein Deficiency.—An acute protein deficiency occurs in association with hemorrhage, extensive burns, intestinal obstruction, paralytic ileus, crush injuries, and extensive infections such as peritonitis. Acute protein deficiency is best treated by immediate transfusion of whole blood and/or plasma. When the loss has been primarily of whole blood, as in frank hemorrhage and in crush injuries, then replacement should be by whole blood. If shock is present, it may be assumed that when the signs and symptoms of shock have disappeared the blood volume has been restored to 70 per cent of the expected normal volume. There are few, if any, indications for the use of red blood cell suspensions in surgical patients, except for certain patients who persistently have reactions to whole blood transfusions in spite of apparent proper cross matching. For the treatment of burned patients, the method of Evans[5] has proved to be a useful one. The amounts of whole blood and/or plasma and the amount of isotonic saline solution to be used in the treatment of the burned patient, are calculated by using the body weight in kilograms and the percentage of the body surface burned. The body weight in kilograms times the percentage of skin surface burned equals the amount of blood or plasma in cc

to be administered Thus a 70 kg man with a 40 per cent burn would be given 2 800 cc of whole blood or plasma in the first 24 hours In addition the patient would receive an equal amount of isotonic saline (2 800 cc) plus the so called basic daily requirement of fluid in the form of 2 000 cc of 5 per cent glucose in water Thus, our patient would receive a total of 7 600 cc of blood and/or plasma, isotonic saline solution and 5 per cent glucose in water in the first 24 hours The total amount of blood and other fluids during the first 24 hours never should exceed 10,000 cc regardless of the extent of burn, *i e*, 4,000 cc of blood and/or plasma, 4,000 cc of isotonic saline solution and 2,000 cc of 5 per cent glucose in water An ideal total caloric intake for a burned patient might be as much as 5,000 calories per day This, of course cannot be achieved by the intravenous route and is seldom attained by the combination of intravenous oral and gastric tube feedings

During the second 24 hours period, the patient receives half the calculated amount of blood plasma, and isotonic saline solution given in the first 24 hours Our 70 kg man with a 40 per cent burn would thus receive 1,400 cc of blood and/or plasma and 1 400 cc of isotonic saline solution plus the basic requirement of 2,000 cc of 5 per cent glucose in water for a total 24 hour intake of 4 800 cc on the second day of the burn

Correction of Chronic Protein Deficiency —The most efficient and least expensive method of correcting a protein deficiency is to feed a patient an adequate balanced diet containing a generous supply of protein The only disadvantage of the oral type of treatment of protein deficiency is the time factor In an adult without gastrointestinal abnormalities infection tumor or blood dyscrasias it may require a number of months to restore adequate protein nutrition If these abnormalities exist it may be impossible to restore adequate nutrition even by the oral route, or a combination of routes in any given period of time Tube feedings of liquid suspensions of ordinary food or protein hydrolysates are frequently useful and at times, lifesaving but such feedings are not as well absorbed and assimilated as natural foods given by mouth Frequently tube feedings produce diarrhea and of course when diarrhea occurs less protein and other food stuffs are absorbed from the gastrointestinal tract

Protein in the form of protein hydrolysates can be administered orally, by Levin tube or jejunostomy tube or by the intravenous route Protein hydrolysates administered by vein is the least efficient means of protein alimentation In addition usually not more than the equivalent of 50 gm of protein can be administered in 24 hours A further limitation of the usefulness of protein hydrolysate administered by vein is the fact that it is impossible to meet the daily caloric requirements by the intravenous route alone When the daily caloric intake is inadequate, the protein may not be available for the replacement or repair of tissues, but will be converted into carbohydrate to provide energy and calories to the body It is not practical to use 10 per cent glucose solution intravenously for more than a few days because it produces obliteration of the superficial veins by thrombosis Three thousand cc of 5 per cent glucose and the equivalent of 50 gm of protein per 24 hours provide only 800 calories per day This is an insufficient number of calories for a healthy adult let alone a patient with a

surgical illness The ideal minimum requirement for a patient postoperatively or a patient with trauma or infection should be 3,000 calories Alcohol cannot be added safely in sufficient quantity to provide an adequate number of calories If a suitable intravenous fat preparation were available, perhaps sufficient calories could be provided to permit adequate utilization of intravenously administered protein At present, however, intravenous protein hydrolysates cannot be used to overcome a protein deficiency

What can be done for a patient with a protein deficiency and a lesion requiring extensive surgery when it is not possible or practical to spend the months necessary to overcome the deficiency by oral feedings? The answer is that the patient should be prepared as rapidly as possible to withstand the trauma of operation and anesthesia with a minimum of risk by the use of whole blood He is thus protected as well as possible against the development of shock and other complications associated with surgical procedures Thereafter, with the necessary surgery accomplished let the patient overcome the protein deficiency by oral feedings When the patient requiring an extensive operation, such as gastric resection or an abdominal perineal resection, has lost more than 10 pounds preoperatively, whole blood should be used The replacement of whole blood preoperatively, (and the immediate replacement of blood lost during the operation) will reduce the possibility of shock during operation due to blood loss or due to minor derangement of cardiac or respiratory function by operation or anesthesia It will also tend to obviate non function of the gastrointestinal tract and delayed soft tissue and bone healing, and it may possibly help to restore normal hormone, antibody, and enzyme production as well as normal lipid transportation

Carbohydrate —Carbohydrate is of importance surgically because it is the simplest and safest means of providing the patient with at least a portion of the daily caloric requirements Carbohydrate is easily prepared and easily administered in the form of 5 per cent glucose in water Fructose solutions can also be used, but apparently offer no advantage over the more readily available glucose

Again, it should be emphasized that for practical purposes the amount of glucose which can be administered intravenously and utilized by the body is limited Three thousand cc of 5 per cent glucose in water within 24 hours will provide only 600 calories The addition of the equivalent of 50 gm of protein in the form of hydrolysates to the fluid would add only 200 calories to this total If 150 cc of 200-proof alcohol are added to the 24 hour intake, then another 1350 calories are added (Only rarely is intravenous alcohol used because of the possibility of intoxication with varying rates of administration and because of tissue necrosis associated with extravasation) With all of these the total caloric intake in 24 hours would be only 2 150 calories Even this grand total is considerably less than the estimated minimum of 2 500 calories per day for the average hospital patient and 3,000 calories for a patient with trauma or infection Calloway and Spector have calculated that a minimum of 2,800 calories per day must be provided before protein can be used for the repair of tissue and not be converted to provide caloric energy[6] As previously stated, 10 per cent glucose in water is seldom used because of its tendency to produce

thrombosis When the intravenous route will be the only available route of alimentation for more than several days 10 per cent glucose in water is impractical because it obliterates the veins available for intravenous administration

It is important to remember that patients who receive only intravenous alimentation, which of necessity is mainly glucose, for more than one or two days should also receive a parenteral thiamin chloride preparation The thiamin chloride is, of course usually administered intravenously as part of a polyvitamin preparation, for reasons described elsewhere (see Chapter 18)

Fats —Excessive body fat increases operative morbidity and mortality Fatty tissues heal poorly and are more susceptible to the development of hematomata, serum collections and infections Obese patients have a high percentage of liver fat The liver with a high fat content is more susceptible to liver injury than a normal liver [7]

Since fat produces approximately twice as many calories per gram as do carbohydrate and protein, fat suspensions for intravenous use have great potential At the present time commercial preparations are available for general use Because of the incidence of hyperpyrexia increasing with the amount of fat so administered, it is not advisable to give more than the equivalent of 50 gm of fat intravenously in 24 hours When intravenous fat preparations are more satisfactory and it is possible to administer more than 50 gm of fat per day, then it will be possible to provide more than 2 800 calories per day and then the protein hydrolysates will for the first time be practical and useful Thus, we still have not been able to achieve complete and adequate intravenous alimentation in the surgically ill patient

Vitamins —Although the various vitamins are discussed in other chapters it is important for the surgeon to understand the major effects of the relative deficiencies of vitamins in the surgical patient The following excerpts are taken primarily from Therapeutic Nutrition as published by the National Research Council [8]

Thiamine —This is necessary for the utilization of carbohydrate by the body and is used up at the rate of 0 5 mg for each 1,000 calories of intake Carbohydrate metabolism is seriously altered before the development of the symptoms of loss of appetite, irritability fatigue neuritic pain and lack of interest in important matters, and these symtoms are present long before the symptoms of beriberi appear According to Syndenstricker[9] a patient may develop a thiamine deficiency in as short a period of time as four or five days when the only nutrient material administered is intravenous glucose

Riboflavin —Riboflavin is required in the oxidative processes of metabolism and there is a close relationship between riboflavin retention and excretion and protein metabolism Apparently riboflavin is necessary for the utilization of protein for repair A riboflavin deficiency will delay wound healing

Nicotinic Acid (Niacin Niacinamide and Nicotinamide) —Like thiamine, nicotinic acid plays an important role in carbohydrate metabolism In addition, like riboflavin it is apparently important in protein metabolism Nicotinic Acid is retained in the body in increased amounts when protein is utilized to overcome a deficit of protein, and when protein is used for repair

These important normal body mechanisms are embarrassed long before symptoms of nervousness, mental depression, loss of appetite, redness of the tongue, ulceration of the gums and diarrhea develop, and these symptoms develop long before symptoms of pellagra appear

Pantothenic Acid —Pantothenic acid acts as a co-enzyme in enzymatic acetylation and it, like riboflavin, is intimately bound up in a protein structure in the body Tissue storage or requirement of pantothenic acid parallels protein intake Experimentally a pantothenic acid deficiency is more readily produced when the diet is high in protein It also appears to be involved in adrenal function Pantothenic acid depletion may lead to adrenal cortical exhaustion

Pyridoxine —The requirements of pyridoxine, like those of pantothenic acid and riboflavin, increase with increased protein anabolism In addition, pyridoxine is involved in normal antibody production and the decarboxylating and deaminating reactions involving various amino acids, as well as having some neutral "fat sparing action"

Folic Acid —This is a hematopoietic and leukopoietic agent It, therefore, serves a purpose in restoring and maintaining the total red blood cell mass and the development of leukocytes, one of the body's defense mechanisms against infection Folic acid probably also has some enzymatic properties which are still unknown

Vitamine B_{12} —Vitamin B_{12} is the potent antianemic substance of the liver It also seems to have an important function in the transmethylation process and may facilitate the marginal intakes of protein

Ascorbic Acid —Vitamin C, as is well known, plays a very important role in therapeutic nutrition It is necessary for the proper formation of all substances having collagen as their basis, and its absence prevents the formation of the matrices of white fibrous tissue, bone, cartilage and dentine For practical purposes, it is not stored in any of the tissues of the body except the pituitary and adrenal glands It has also been demonstrated that animals deficient in vitamin C develop a more profound degree of anesthesia and are much slower to recover from a given amount of an anesthetic agent than animals not deficient in vitamin C

Vitamins D and K —There is little need for supplementary vitamin D in the adult, with the exception of those patients with fractures of bone The usefulness of vitamin D in treating infants and children, of course, is well known Vitamin K is required in special instances, the causes and effects of vitamin K deficiency and the proper use of the various therapeutic vitamin K preparations need not be discussed here

Requirements for Vitamins —The importance of vitamin therapy in seriously ill surgical patients might be emphasized in a simple analogy It is, of course, useless to supply abundantly, lumber, steel and bricks for the repair of a damaged building if hammers, nails, bolts and cement are not available to fashion the former materials into a functioning part of the building It is just as foolish to provide carbohydrate, fat protein and potential calories in the presence of subclinical vitamin deficiencies and expect the body to restore a functioning part or parts of the body efficiently

What are the indications for supplementary or therapeutic vitamin administration? An excellent answer to the question has been provided in

the pamphlet "Therapeutic Nutrition"[8] published by the Medical Research and Development Board of the Department of Defense of the National Research Council. The rules are in essence as follows. (1) When a previously healthy patient has a minor illness expected to last less than ten days and is ambulatory and eating well with no history of previous inadequate nutrition, no special consideration need be given to his vitamin requirements, (2) when the foregoing qualifications are not met, the patient is given one to two times the daily requirement of vitamins each day. (3) when the patient receives all of his nutrition by the intravenous route he is to receive one to two times the minimum requirement for parenteral injection together with additional supplement of vitamin C. (4) when a serious illness or severe trauma or burn exists the requirement for the first few days is five to ten times the recommended daily requirement of a multiple vitamin preparation. Thereafter the patient should recieve two to three times the minimum daily requirement until recovery is complete. The proposed formula for standard daily requirement (maintenance) vitamin capsule or tablet is a follows

Thiamine	2 mg	Calcium Pantothenate HCl	2.0 mg
Riboflavin	2 mg	Folic Acid	1.5 mg
Niacinamide	20 mg	Vitamin B_{12}	2.0 mcg
Ascorbic Acid	75 mg	Vitamin A	5000 units
Pantothenic Acid	18 mg	Vitamin D	400 units
Vitamin K		2 mg	

For intravenous, subcutaneous or intramuscular use when the patient receives his alimentation by the parenteral route the following basic formula is recommended

Thiamine	10 mg	Calcium Pantothenate	20 mg
Riboflavin	5 mg	Pyridoxine HCl	20 mg
Niacinamide	50 mg	Folic Acid	[illegible] mg
Vitamin B_{12}		15 mcg	

Vitamin C in amounts up to 1 gm. daily and vitamin K are administered as indicated. The Committee stated that there was no indication for having available single vitamin preparations except for vitamins C, K, and B_{12}.

Salt and Water Balance.—Water balance or the maintenance of the body fluids—intracellular and extracellular including interstitial and intravascular—is of the utmost importance to the surgical patient. Water balance is a complex problem. It cannot be divorced from electrolyte metabolism because the retention of water is so largely dependent upon the amount of sodium in the body. On the other hand the loss of sodium and chloride is dependent upon the presence of water to carry it away.

Reduced to the simplest terms normal water balance in the healthy adult is dependent upon absorption of water from the gastrointestinal tract, the water produced by the metabolic processes of the body and the loss of water by vaporization urination defecation and perspiration. Sources of water are (1) ingested liquids, (2) the water of semisolid and solid foods,

and (3) the water produced by oxidation of foodstuffs and of body tissues In spite of the fact that from 7 000 to 10 000 cc of fluid gain entrance to the gastrointestinal tract daily in drinks, food, and secretions, only about 150 cc of water is excreted in the stools This is largely due to reabsorption of water in the small intestine and to the dehydrating action of the large bowel

Normal oral intake under average conditions varies from 800 to 3,000 cc per day The solid and semi solid food of average diets yield from 1,000 to 1,500 cc of water per day, since such foods contain approximately 70 per cent water The third source, oxidation of foodstuffs and body tissues adds from 200 to 400 cc The oxidation of 1 gm of carbohydrate or of 1 gm of protein yields approximately 1/2 cc of water, the oxidation of 1 gm of fat produces 1 cc of water The water content of solid food plus the water produced by oxidation of the food is equivalent to about 0 9 cc per gm of solid food

The insensible loss, or loss by vaporization amounts to between 1,000 to 1,500 cc daily Ordinarily, 25 per cent of the body heat is dissipated by means of sweat With the appearance of visible sweating as much as 100 per cent of the excess body heat may be dissipated by vaporization from the skin There is always water vapor in the expired air The amount of vaporization of water by the lungs and skin is not dependent on the amount of water available Lungs and skin have priority over kidneys for available water The kidneys, on the other hand, are markedly affected by the amount of water available Thus, perspiration may continue in the dehydrated patient even after the kidneys have stopped functioning because of lack of available water

TABLE 141 —MINIMUM REQUIRED URINE OUTPUT (AFTER LASHMET AND NEWBURGH[13])

Kidneys	*Maximum concentrating ability specific gravity*	*Minimum amount of water in cc required to excrete 35 gm of waste material*
Normal	1 032–1 029	473
Diseased	1 028–1 020	595
	1 024–1 020	605
	1 019–1 015	850
	1 014–1 010	1439

The kidneys of a healthy adult excrete 35 gm of dissolved solid material per 24 hours Normal kidneys which are able to concentrate to a specific gravity of 1 030 require a minimum of approximately 500 cc of water as urine to excrete this amount of solid material Kidneys which concentrate to 1 012 require 1,500 cc (Table 141) In the presence of tissue damaged by toxins, infection, or trauma of operation, the solid material excreted by the kidneys may increase considerably above the normal 35 gm If therefore one maintains an output of 1,000 cc of urine in a patient with normal kidneys there should be sufficient volume to carry away the increased amount of solid material It is safe to assume that the average surgical patient is in water balance if the daily urine volume is approximately

1 000 cc provided that repeated urinalyses show no evidence of renal damage A patient with kidney damage may need more than 1 500 cc of urine for elimination of solid material

To summarize then the normal 24 hour output of water by insensible loss is from 1 000 to 1 500 cc , by urine from 850 to 1 500 cc and by feces 150 cc The total is therefore from 2 000 to 3 150 cc daily Intake of water per day is as follows by mouth as liquid—from 800 to 1 500 cc by mouth as part of solid foods from 1 000 to 1 500 cc and by oxidation of foodstuffs from 200 to 400 cc It follows therefore that a surgical patient with normal kidneys should have at least 1 500 cc and preferably 2 500 cc of fluid intake per day If losses of fluid are excessive a larger amount of fluid will be required Table 142 gives some of the factors which must be accounted for in calculating the fluid requirements of the surgical patient

TABLE 142 —CALCULATION OF DAILY WATER REQUIREMENTS

	cc average variations
Uncomplicated cases	
For vaporization	1000 1500
For urine	1000 1500
	2000 3000 fluid required
Complicated cases (sepsis elevation of temperature humid weather renal damage)	
For vaporization	2000 2500
For urine	1000 1500
	3000–4000 fluid required
Seriously ill patients with drainage	
For vaporization	2000
For urine	1000
For replacement of body fluid losses	
1000 cc bile drainage	1000
3000 cc Wangensteen drainage	3000
	7000 fluid required

Sodium Chloride Requirements The average American diet contains from 137 to 205 m Eq of sodium chloride per day (8 to 12 gm) In order to compensate for salt losses in the perspiration and feces to facilitate acid base adjustments and to maintain body fluid the patient s daily intake of salt should be from 85 to 171 m Eq (5 to 10 gm)[10] One liter of isotonic sodium chloride solution (0 9 per cent) will provide 154 m Eq (9 0 gm) of sodium chloride Some authors prefer to administer the required sodium chloride in the form of 1/3 isotonic solution (0 3 per cent) Normally an excess of salt is excreted by the kidneys either as sodium or chloride or both If salt intake is reduced for more than four days the kidneys may conserve salt to such an extent that they will excrete as little as 6 m Eq (0 3 gm) per day

When chloride (the predominant acid element of gastric juice) is lost in a greater amount than sodium (the predominant basic element) as in vomiting the kidneys tend to retain chloride and excrete sodium A chloride loss produces first a hypochloremia and second a general deple-

tion of the tissue cell chlorides This is often followed by an alteration in the acid base balance, and later by an increase in the non protein nitrogen of the blood When basic elements are lost as by duodenal fistula or diar rhea sodium is retained and chloride excreted Thus in the presence of a normal amount of fluid and an excess of sodium chloride, normal kidneys attempt to preserve the acid base balance of the body If salt intake is insufficient fluid intake is low, the kidneys are deficient, or loss of either aci or basic substances is excessive, then acid base balance may be altered i spite of the compensating action of the kidneys The presence of sever of these factors in the same patient may produce such profound chang in the equilibrium of the blood that death may follow Moderate changes will produce significant alterations of various body functions (i e see Edema and Protein Deficiency) It is therefore the duty of the surgeon to provide sufficient fluid and just sufficient salt to prevent excessive electrolyte deficits

Potassium —The importance of potassium therapy was first recognized by Darrow[10] in the treatment of infantile diarrhea The body contains twice as much potassium as sodium Potassium is found predominantly in tissue cells Potassium appears to be essential (as an adequate caloric intake is essential) for the utilization of protein and the maintenance of a positive nitrogen balance The tissues represent about four fifths of the body weight Sodium of course is found primarily in the extracellular fluids of the body which make up approximately one-sixth of the body weight In dehydration there is some exchange of potassium to the extra cellular fluid and of sodium to the body cells Therefore it is obvious that one cannot determine the concentration of potassium in the cells by meas uring the concentration of potassium in the blood serum However certain useful information can be obtained by determining the serum potassium concentration

Normally the potassium concentration of the serum is 3 5 to 5 5 mEq per liter (1 gm of potassium equals 25 3 mEq) A low serum potassium level hypokalemia may produce no clinical symptoms or it may be asso ciated with weakness anorexia nausea vomiting, listlessness apprehension diffuse pain drowsiness stupor and irrationality Either high or low serum potassium levels may be suspected by changes in electrocardiographic tracings The electrocardiographic tracing will usually show evidence of a dangerously high serum potassium level but does not always suggest a seriously lowered potassium level

For 24 to 48 hours after an acute severe infection after trauma of surgery or accidental trauma there is an increase in potassium and nitrogen excretion in the urine It is interesting to note that kidneys will excrete potassium even when a deficiency of potassium exists (When a sodium deficiency exists the kidneys conserve sodium by decreasing the rate of sodium excretion in the urine) A presumptive diagnosis of a potassium deficiency can be made without the aid of a serum potassium level deter mination if the patient has hypochloremic alkalosis—an increased serum carbon dioxide concentration and a decreased serum chloride concentration The serum magnesium changes are similar to those of potassium and are

now under study However, it would appear, at present, that magnesium therapy is not necessary

Fluid and Electrolyte Therapy —Fluids may be administered by the oral, rectal, subcutaneous, intramuscular, and intravenous routes and by Levin tube, jejunostomy tube, *etc* The rectal, subcutaneous, and intramuscular routes are seldom used today in the treatment of adult patients Obviously all surgical patients do not need intravenous fluid Whenever possible, fluids should be taken orally Either 5 per cent glucose in water (nearly isotonic) or 5 per cent glucose in isotonic saline solutions are the fluids commonly used intravenously Excessive amounts of water may lead to

Average Concentrations in mEq/L

	Na	Cl	K
GASTRIC JUICE	60 4	84 0	9 2
BILE	148 9	100 6	4 98
PANCREAS	141 1	76 6	4 6
SMALL BOWEL *continuous suction*	104 9	98 9	5 1
ILEOSTOMY - *recent*	129 4	116 2	11 2
ILEOSTOMY *adapted*	46 0	21 4	3 0
CECOSTOMY	52 5	42 5	7 9
DIARRHEA *(children mEq/day)*	11 6	8 0	17 5

Fig 66 —Sodium chloride and potassium concentrations of various intestinal juices

water intoxication as described by Helwig[11] Five per cent glucose in isotonic saline solution is hypertonic and causes slightly more thrombophlebitic reactions than do isotonic solutions Ringer's solution and Hartman's solution may also be used Ringer's solution contains calcium and potassium in addition to sodium chloride Hartman's solution contains sodium lactate, in addition to the constituents of Ringer's solution Hartman's solution is especially useful in the treatment of persistent acidosis Ten per cent glucose occasionally is used either in an attempt to produce diuresis or to increase the caloric intake Hypertonic solutions of sodium chloride in concentrations as high as 3 0 per cent may be given to combat hypochloremia Insulin vitamins digitalis alcohol ammonium chloride *etc* may be added if indicated It should be borne in mind that parenteral glucose administration employed as the only source of alimentation should be supplemented by adequate amounts of thiamine chloride as previously mentioned

As a basic rule, each patient should receive a minimum of from 2,500 to 3 500 cc of fluid daily, provided the patient has normal kidneys and does not have excessive sweating or abnormal losses of fluid or electrolytes A generally safe rule of thumb (except during the day of operation and the first postoperative day, when a slightly lower amount is acceptable) is that the patient should excrete approximately 1,000 cc of urine daily Because of the tendency to retain sodium and water after operation or trauma the patient should not receive excessive amounts of sodium chloride for the first 48 hours after operation In this period and in the absence of excessive fluid loss usually no sodium chloride or only 500 cc of 0 9 per cent sodium chloride is used (4 5 gm or 77 m Eq) If there are abnormal fluid losses, the estimated sodium chloride equivalent lost must be replaced in the intravenous fluids (Figure 66)

In an uncomplicated postoperative patient who will probably be able to take fluids in 24 hours, 1,500 to 2,500 cc of 5 per cent glucose in water will provide sufficient fluid and will supply some of the caloric needs of the patient If the patient will obviously require intravenous fluid for a number of days then the basic daily fluid replacement should contain 60 m Eq of potassium and 154 m Eq of sodium chloride on the third day and daily thereafter

Chloride replacement with sodium chloride is made on the basis of the clinical condition of the patient If the serum chloride level is only slightly less than the minimum normal value of 98 m Eq per liter and the patient has none of the signs and symptoms of hypochloremia, then only the daily requirement of sodium is administered When marked deficiencies occur, it is sometimes useful to have a rough estimate of how much sodium chloride in addition to the daily requirement will be necessary to restore the serum chloride level to a normal or relatively normal value Since the extracellular fluid of the body is approximately 15 per cent of the body weight, multiplying 0 15 (15 per cent) times the body weight in kilograms times the number of milliequivalents the observed serum chloride is below the average normal will give a very rough estimate as to how many extra milliequivalents of chloride will be required to overcome the chloride deficiency It should be remembered that the amount given to overcome the deficiency should be given in addition to the daily requirement Large amounts of sodium chloride, when indicated, may be administered intravenously as 2 or 3 per cent sodium chloride in water

Any patient who has Levin tube suction or diarrhea of more than two days duration will probably require potassium therapy Potassium should never be administered intravenously to a patient with poor renal function, because the potassium will be retained in the body and reach toxic levels When fluids containing sodium chloride and potassium chloride are administered to individuals with hypochloremic alkalosis the serum potassium level will usually be normal when the serum carbon dioxide value returns to normal

Nutrition and Wound Healing —The management of the patient and his wound may aid or hinder the physiological processes leading to the fibroblastic fusion of the wound surfaces The effect of proper or improper management is especially evident during the lag period of wound healing—

the first three, four or five days of healing The normal physiologic factors of wound healing have often been pushed into the background by extensive considerations of skin preparations, aseptic techniques, and suture materials The age of the patient, the nature of the disease, and the disturbances in body chemistry brought about by disease have all too often been given but scant attention Nutritional considerations in wound healing must include (1) hydration of the tissues, (2) distribution of body electrolytes, and (3) the amount of available protein vitamin C vitamin K and other vitamins Dehydration and overhydration profoundly alter the condition of wound surfaces and the composition of wound space contents Edema or over hydration and dehydration cause a prolongation of the lag phase of wound healing Patients who require extensive surgery and who will not respond to a high protein diet should be treated with transfusions of whole blood or plasma if they show clinical signs of malnutrition, their serum protein concentration is lowered or if the blood volume is reduced Numerous investigators have demonstrated the inhibitory effect of vitamin C deficiency upon wound healing The incident of low plasma vitamin C levels in a group of medical students as reported by Rinehart indicates that the population as a whole does not maintain an optimum vitamin C level He has also shown that several common surgical conditions are associated with very low vitamin C levels

Following extensive operative procedures or in conditions known to be associated with low vitamin C levels, the parenteral or oral administration of vitamin C is *necessary to insure good wound healing* One hundred mg of ascorbic acid daily is usually sufficient

A vitamin K deficiency with the *resultant prothrombin deficiency* may so reduce the efficiency of the clotting mechanism as to threaten the life of the surgical patient by hemorrhage Although the life of the patient may not be seriously jeopardized by it a prothrombin deficiency may profoundly alter the normal course of wound healing Oozing capillaries distend potential wound spaces with blood and although the hemorrhage may not be serious this delays wound healing and exposes the wound to serum collections and infection The presence of jaundice or suspected liver damage immediately demands a determination of the prothrombin time If this reveals a deficiency it must be treated with vitamin K and bile salts or with a parenteral vitamin K preparation until the underlying condition has been corrected

Preoperative and Postoperative Feeding —It is desirable that the stomach be empty at the time of operation In all elective operations therefore, nothing is administered by mouth for at least eight hours prior to operation If the patient is dehydrated, acidotic or alkalotic suitable parenteral solutions must be administered during the preoperative period The principal danger of retained food in the stomach is the possibility of aspiration of vomitus during anesthesia or recovery from anesthesia In emergency operations it is wise especially in children to aspirate the stomach with a tube before the anesthetic is administered Food retained in the stomach at the time of operation may also increase the possibility of postoperative gastric retention gastric dilatation, and may interfere seriously with the technical part of the operation itself Postoperative distention in many

instances may be reduced or avoided by emptying the colon with a good cleansing enema prior to operation

Although it is best to avoid a period of starvation immediately after the body metabolism has been disturbed by operation, patients whose nutrition has not been impaired before operation suffer no great loss in two days of abstinence from semi-solid or solid foods After uncomplicated abdominal operations, water by mouth should be withheld until active peristalsis is heard Prior to this time fluids are administered parenterally When active peristalsis has been demonstrated, water is ordered in small amounts usually an ounce every hour for the first four hours If this is well tolerated, the amount of water is gradually increased until unrestricted quantities are retained Then a full liquid diet is administered If a full liquid diet is tolerated, the patient is allowed a soft diet and then, in turn, a normal diet On such a carefully supervised plan some patients may after an abdominal operation tolerate a normal diet on the morning of the second postoperative day

Diets Used in the Department of Surgery University of Pennsylvania Hospital

Surgical Liquid Diet —This diet consists of clear liquids It is inadequate in all of the essential food elements It is given at frequent intervals to relieve thirst and to supply a few calories and small amounts of sodium and potassium chloride

Foods Permitted —Broth, tea and coffee with sugar, water

Liquid Diet This consists of foods which are liquid at body temperature It supplies enough calories for maintenance requirements if an adequate intake can be secured It is deficient in iron and nicotinic acid

Foods Permitted Broth, strained soups, strained fruit juices, cereal gruel, milk and cream, custards and junket, clear gelatin, plain ice cream, eggnog, cocoa, tea, coffee, ginger ale, sugar, and supplemental feedings of proprietary protein or milk preparations

Sample Menu

Breakfast	*Dinner*	*Supper*
Apricot nectar	Chicken broth	Cream of carrot soup
Farina gruel with milk	Ice cream	Custard
Coffee	Tea	Tea
Milk	Milk	Milk
10 00 A M	*2 00 P M*	*8 00 P M*
Jello with milk	Junket	Jello with milk
Eggnog	Protenum	Protenum

Bland Soft Diet

Six Small Meals —This modification of the bland diet is used when frequent small meals are desirable It is given postoperatively when a subtotal or total gastrectomy is performed where it is necessary to reduce the quantity of food taken at meals, keep some food in the stomach at all times and still maintain the adequacy of the diet It provides approximately 90 gm of protein, 80 gm of fat 270 gm of carbohydrate and 2,100 calories Bulky, high residue foods

should be avoided as much as possible Vitamins are supplied for specific deficiencies The use of "Tween 80" a dispersing agent, to improve fat absorption has been advocated It is given orally in doses of 40 to 50 mg for each gram of fat The bland soft diet is served as follows

Breakfast	*Dinner*	*Supper*
Stewed fruit or fruit juice Refined cereal with ½ cup of milk Coffee or tea	Lean meat fish or other protein Potato or substitute Pureed vegetables ½ slice of bread with butter	Meat fish or other protein Pureed vegetable ½ slice bread ½ cup of milk Dessert stewed fruit, Jello junket, pudding custard, ice cream or plain cookies or cakes
10 00 A M	*2 30 P M*	*8 00 P M*
One egg 1 slice of toast with butter ½ cup of milk Clear jelly	Sandwich, plain or toasted cream cheese, cottage cheese jelly smooth peanut butter, chicken, tuna or salmon ½ cup of milk Dessert stewed fruit Jello, junket, pudding, custard, ice cream or plain cookies	Cereal with milk ½ cup milk Dessert same as 2 30 P M feeding

Jejunal Feeding —Jejunal feeding is at present seldom necessary in gastrectomy patients who are adequately prepared for surgery If difficulty with nutrition is anticipated a two lumen tube may be placed at the time of operation which will permit feeding into the jejunum at the same time as suction is maintained on the stomach to prevent any pressure from being built up behind the anastomosis in this area For jejunal feeding, commercial homogenized milk as an ideal food has been advocated by Zollinger [13] This can be increased to a high caloric formula containing dextrin as carbohydrate to reduce the osmotic activity of the mixture Ordinary food that has been liquified by means of a Waring Blendor can be introduced through the jejunostomy tube this will often prove of benefit in controlling the diarrhea (See also Standard Tube Feeding page 607)

Minimum Residue Diet (See page 630) —This diet is used preoperatively when it is desirable to reduce the fecal residue to an absolute minimum This diet is inadequate in all of the food elements except protein The foods permitted are

Meat or liver, lean Meat broths
Eggs, preferably hard boiled
Cottage cheese
White rice, Farina and Cream of Wheat
Gelatin
Coffee and tea
Sugar, dextrose and corn syrup

Sample Menu

Breakfast	*Dinner*	*Supper*
Farina	Chicken broth	Roast chicken
Hard boiled egg	Broiled liver	Rice
Coffee with sugar	Rice	Cottage cheese salad
	Cherry Jello	Lemon Jello
	Tea with sugar	Tea with sugar

Low Residue Diet.—This diet is used postoperatively when it is desirable to keep the quantity of fecal residue low. It is adequate in all respects and will provide approximately 80 gm. of protein, 70 gm. of fat, 360 gm. of carbohydrate, and 2,000 calories. The following items are included in each days' diet:

Meat, poultry or fish—two average servings
Eggs—two
Vegetables, green or yellow, cooked—two servings
Potatoes or substitute—two servings
Fruit, other than citrus, cooked—two servings
Bread, white only—six slices
Cereal, refined—½ cupful
Milk, boiled—one pint
Butter—4 level teaspoonfuls

Foods Permitted.—*Soups*—any strained soup, cream soups may be served if the milk is counted as part of the total daily allowance. *Meat*—Beef, lamb, lean pork, veal poultry (without skin), fish, shellfish, liver at least once a week. May be baked, boiled, broiled or roasted. It may be advisable to grind the meat before serving. *Eggs*—any style except fried. *Vegetables*—any that can be passed through a sieve, potatoes without skins. *Fruits*—juices except those of citrus fruits, canned or cooked fruit with skins and seeds removed, ripe bananas. *Bread and Cereals*—White bread, plain or toasted, plain rolls, white crackers. Refined cereals such as Corn Flakes, Cream of Wheat, Puffed Rice, Rice Krispies, macaroni, noodles, spaghetti, rice. *Milk*—boiled, one pint daily as beverage or used in cooking. Any mild cheese. *Desserts*—Plain ice cream, fruit ices (except citrus fruits), gelatin, junket, puddings, plain cakes and cookies. *Sweets*—Candy without nuts or fruit, honey, jelly, molasses, sugar, and syrups. *Beverages*—Coffee, tea, cocoa (if made from part of milk allowance), ginger ale, carbonated beverages. *Fats*—Butter, margarine, mayonnaise, and olive oil as desired. *Forbidden Foods*—Citrus fruits and juices, unsieved vegetables, whole grain bread or bran products, milk in excess of one pint daily, luncheon meats of all types, sausage, pie, pastry, nuts, fried foods of any kind.

Sample Menu

Breakfast	*Dinner*	*Supper*
Apricot nectar	Chicken broth	Sliced white meat of turkey
Farina	Lamb patty	Cranberry jelly
2 soft boiled eggs	Mashed potatoes	Baked potato
2 slices of toast with butter and jelly	Green bean purée	Pea purée
1 cup of boiled milk	Canned pear	Floating islands
Coffee with sugar and cream	White bread with butter	White bread with butter
	½ cup of boiled milk	Tea with sugar
	Tea with sugar	½ cup of boiled milk

Low Fat Diet.—This diet will supply approximately 75 gm of protein, 20 gm of fat, 350 gm of carbohydrate and 2,000 calories. It is given in conditions requiring surgery such as cholecystitis or cholelithiasis both pre- and postoperatively when the patient is able to tolerate all foods except those that are gas forming or those that might have a high content of unemulsified fats. It is composed of the following foods and should include daily at least the indicated amounts of each:

- Lean meat, poultry or fish—two average servings
- Potato baked, boiled or mashed or macaroni, noodles or rice—two average servings
- Other vegetables (except those that might produce gas in the intestine)—three servings
- Citrus fruits—one serving
- Other fruits (except melons)—two servings
- Bread—four slices
- Cereal, whole grain or enriched—one serving
- Skim milk—one pint to one quart
- Syrup, sugar, honey or jelly—unlimited
- Pot cheese—unlimited
- Sponge cake or plain vanilla wafers—as desired

Sample Menu

Breakfast	*Dinner*	*Supper*
Orange juice	Beef broth	Roast chicken
Cornflakes with skim milk and sugar	Fillet of pollock	Mashed potatoes
2 slices of plain toast with jelly	Baked potato	Peas
Black coffee with sugar	Stewed tomatoes	Shredded carrot on sliced pineapple on lettuce leaf
1 cup of skim milk	Canned Apricots	Sponge cake with strawberries
	Plain bread with jelly	Plain bread with jelly
	1 cup of skim milk	1 cup of skim milk
	Tea with sugar	Tea with sugar

Standard Tube Feeding (See Chapter 21, page 607).—This feeding will furnish approximately 82 gm of protein, 60 gm of fat, 178 gm of carbohydrate and 1,580 calories. It consists of the following items:

Skim milk powder	½ measuring cup
Dextri Maltose	½ measuring cup
Polyvitamin dispersion	½ teaspoon
Eggs	4
Milk, Whole	960 cc

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Chapter 33

Nutrition in Ophthalmology

By J J Stern

CONJUNCTIVA, CORNEA AND SCLERA

Vitamin A Deficiency

Signs and Symptoms.—The ocular changes due to vitamin A deficiency range from simple xerosis conjunctivae to the fully-developed picture of keratomalacia The latter type is hardly ever seen any more in economically sound countries Xerosis is more frequent, particularly in undernourished infants where improper diet after weaning is a common cause of its appearance

In xerosis conjunctivae, the bulbar conjunctiva presents a peculiar dry aspect, described as "lack of luster" Light reflection from the conjunctiva is interfered with This becomes easily detectable when the lids are kept open for ten to twenty seconds In the very early stages, the conjunctival changes are patchy, becoming confluent when the condition progresses The deeper conjunctival and episcleral vessels take on a bluish tinge or become invisible because of the diminished transparency of the epithelium Loss of elasticity causes a wrinkling of the conjunctiva which can be provoked by pushing the bulbar conjunctiva towards the limbus with a finger pressed over the lower lid Later the folds appear spontaneously, forming concentric circles and showing dry, lusterless tops and moist furrows when the eyes are moved sideways

Another common sign is the appearance of Bitot s spots white elevated sharply outlined patches not wetted by tears and covered with material resembling dried foam They are usually triangular in shape the base facing the limbus, and most frequently occupy the temporal side of the conjunctiva, within the lid aperture The foam-like substance can be scraped away but reforms It consists of epithelial debris fatty globules and frequently masses of xerosis bacilli The latter are saprophytes and have neither diagnostic nor etiologic significance

In the Orient a certain type of conjunctival pigmentation has been described in avitaminosis A [1-8] It first occupies the lower part of the bulbar conjunctiva the lower fornix and the semilunar folds these areas become yellowish, then gray, finally bluish mauve Later on the same changes may appear in the upper lid and fornix The pigment is melanin, and it usually remains for some time after all other evidence of the condition has responded to therapy

A smoky discoloration of the bulbar conjunctiva attributed to vitamin A deficiency, has been described in colored races It is due to an outward

migration of chromatophores from the limbal pigment ring[1] The same phenomenon has been produced experimentally in rabbits fed a diet deficient in vitamin A Only animals with pigment showed it, there was no development of new chromatophores[2]

In severe cases of xerosis all signs are accentuated The bulbar conjunctiva becomes thick, opaque, thrown into large folds and furrows At the same time the cornea becomes involved The first signs here are loss of luster, dryness on exposure to air, and reduced sensitivity The latter suggests nerve involvement and will be discussed later When the condition progresses unchecked, patchy areas resembling Bitot's spots appear on the cornea, sometimes as a continuation of the conjunctival spots, sometimes as crescents along the limbus, and occasionally as isolated areas in the center If the process advances further, true keratomalacia sets in The cornea becomes dull, central or peripheral infiltrates form, and the periphery becomes vascularized The epithelium over the infiltrates is shed, ulcers form and become infected, and the cornea finally perforates The vascularization of the cornea is morphologically different from that seen in riboflavin deficiency and may be secondary to necrosis of the corneal epithelium

Kruse[3] described the occurrence of conjunctival spots in chronic vitamin A deficiency in a large number of seemingly healthy subjects The lesions are "grossly perceptible elevated spots of distinctive color and characteristic location" They disappeared or at least receded after many months' treatment and with very large doses of vitamin A (100,000 units daily) It is noteworthy that only few subjects showed high adaptometer readings and most of them had normal blood vitamin A levels Whether the lesions described by Kruse are senile or presenile alterations, or are due to chronic mild vitamin A deficiency remains to be proven

Diagnosis —Xerosis or thickening of the conjunctiva is one of the early signs of avitaminosis A This was confirmed in a nutritional survey in Newfoundland,[4] where thickening of the conjunctiva was observed to be very common in children of grade school age, and always associated with low serum vitamin A levels Four years later, the same observers found a statistically significant improvement in the same age group Within those four years, the government had introduced the fortification of oleomargarine with vitamin A and the enrichment of bread

There is some evidence of lack of correlation between dietary intake of vitamin A or vitamin A blood level and conjunctival lesions[5,6] Likewise, large doses of vitamin A, given over a period of two years, failed to influence various degrees of opaqueness of the conjunctiva and pinguecula-like spots in a group of subjects[7,7a] The most recent and probably most comprehensive experimental work done on human volunteers[8] resulted in the same negative findings no conjunctival or corneal changes occurred after up to 25 months of vitamin A depletion, in spite of an early drop in the carotenoid level of the blood and a drop of the vitamin A level after about eight months This discrepancy between clinical and experimental findings will have to be explained before a final evaluation of the situation can be made It is not unlikely that here, as in other vitamin deficiencies, conditioning of the organism or the conjunctiva by unspecific factors plays a role in the production of clinical signs of vitamin A deficiency

Pathogenesis —The mechanism of the epithelial damage in vitamin A deficiency is by no means clear. Anatomically, the changes can be described as atrophy of the epithelium, reparative proliferation of the basal cells, and growth and differentiation of these new products into a stratified keratinizing epithelium.[9] In avitaminosis A the mitotic rate of a healing corneal wound is reduced by 30 per cent.[10] The mechanism has been claimed to be essentially neurotrophic. Of particular interest are degenerative changes in the myelin sheath of the trigeminal nerve,[11] reduced corneal sensitivity in xerosis and the finding of thickened corneal nerves at an early stage of the disease,[1] together with degeneration of the Gasserian and ciliary ganglia.[13] Thus, peripheral nerve involvement may play an important role in the pathogenesis of xerophthalmia.

Prevalence —Xerosis conjunctivæ is not infrequently seen in patients suffering from liver disease—particularly in infants who have not yet accumulated stores of vitamin A in the liver—because the diseased organ is unable to store or mobilize vitamin A.

While keratomalacia is practically unknown in economically sound communities, where even simple xerosis is uncommon, it causes havoc in large areas of the Orient and other regions where severe malnutrition is prevalent. Keratomalacia was frequent in Malaya before World War II because condensed milk was so cheap that many mothers substituted it for breastfeeding. During the Japanese occupation, when condensed milk was unobtainable, breastfeeding was resorted to, and keratomalacia almost disappeared. Now, with condensed milk available again, the incidence of keratomalacia is once more on the increase.[14]

Treatment —(*a*) *Preventive Treatment* —An allowance of 5 000 i u (based upon two thirds as carotene) daily for normal adults has been adopted in the List of Recommended Daily Allowances.[15] The Medical Research Council of Great Britain[8] recommends 2 500 i u daily as a minimum maintenance dose.

(*b*) *Curative Treatment* —Deficiency signs make their appearance only if and when the body stores of vitamin A have reached a very low level. In order to replenish the depleted stores at a fast rate, it is advisable to administer the vitamin in amounts far greater than the maintenance requirement. It is therefore the general practice to give 25 000, 50 000 or even 100 000 i u daily, until results are obtained. Treatment has to be adapted to special conditions like liver disease or intestinal disorders. Where utilization of dietary carotene is impaired, it is advisable to substitute preformed vitamin A for carotene.

(*c*) *Local Therapy* —Vitamin A and carotene have been used locally in a number of eye conditions, such as corneal injuries, superficial neuroparalytic and interstitial keratitis, and Mooren's ulcer. Local therapy with vitamin A does not seem rational, and should be replaced either by systemic administration of vitamin A, if a deficiency is suspected, or by appropriate local treatment.

Ariboflavinosis

Signs and Symptoms —Corneal vascularization is probably the earliest and most constant sign of riboflavin deficiency. Its development is pre-

ceded by injection of the bulbar and palpebral conjunctiva and the fornix, circumcorneal injection, and engorgement of the limbic plexus Later, there may be superficial and interstitial infiltration of the cornea, sometimes patchy, sometimes diffuse Finally, congestion of the sclera, and even of the iris, may occur The subjective symptoms include itching and burning, roughness of the eyes, photophobia, and impairment of visual acuity In the more commonly observed early stages, the discrepancy between the patient's complaints and the paucity of clinical signs is characteristic

The diagnosis is facilitated by the presence of other clinical signs of ariboflavinosis cheilosis, glossitis and dyssebacia

Pathology —Corneal vascularity is a compensatory process bringing blood into closer contact with the deeper layers of the corneal epithelium when the cornea is suffering from riboflavin deprivation The corneal epithelium shows a surprisingly high metabolic rate, while that of the stroma is relatively low [16–19] Riboflavin, as the phosphoric acid ester, in combination with adenylic acid, forms a flavin-adenine-dinucleotide which is the prosthetic group of Warburg's yellow respiratory enzyme It acts as dehydrogenase in anaerobic glycolysis, maintaining a process of anoxybiotic fermentation This mechanism is essential for the respiratory process of the cornea and other avascular tissues

The oxygen consumption of the cornea of riboflavin deficient rats is lowered When vascularization of the cornea is present, the oxygen uptake of the corneal stroma is elevated, in the absence of vascularization it is rather low The increased oxygen uptake of the stroma must therefore be the result of the vascularization, and perhaps of the cellular infiltration

Differential Diagnosis —Circumcorneal injection is undoubtedly an early sign of ariboflavinosis, but it also occurs in many other ocular disturbances Thus, riboflavin cannot be expected to exert a therapeutic influence on every case of circumcorneal injection Familiarity with the variations of the normal limbus as visualized by the slit lamp is essential for the detection of corneal vascularity a condition in which newly formed blood vessels leave the limbic plexus and centripetally enter the subepithelial space of the true cornea This state, and nothing less, is acceptable as corneal vascularity

The limbus is not a line, but a band about one millimeter wide This area is plentifully provided with blood vessels which comprise the limbic plexus This plexus is not always visible in the living eye, as the vessels are frequently empty and cannot be seen The plexus responds readily to mechanical or chemical irritation that causes conjunctival hyperemia and opens the vessels of the limbus This hyperemia is entirely non specific The sprouting out of new vessels from the limbic plexus is preceded by engorgement and increased activity of the plexus itself This condition will or will not respond to riboflavin administration, according to its etiology For practical clinical purposes it must be insisted upon that vessels appear in the cornea before one can speak of corneal vascularity

The corneal vascularity of well-developed riboflavin deficiency always occurs in the entire circumference of the cornea This fact is important for correct diagnosis Both eyes usually show equal vascularity, but there

are exceptions to this rule Disease or trauma may condition vascularization of the cornea of one eye when the degree of riboflavin deficiency is insufficient to produce signs in the other eye

Invasion of the cornea by blood vessels occurs in several pathologic conditions In rosacea keratitis it is usually most marked in the upper quadrants of the cornea and preceded by subepithelial infiltrates which progress towards the center of the cornea and the deeper layers of the stroma Eventually the epithelium over these areas becomes eroded and the ensuing ulcers attract blood vessels which form a vascularization of the fascicular type This clinical picture is different from that of the ariboflavinotic type of corneal vascularity There is disagreement in regard to the beneficial effect of riboflavin in rosacea keratitis claimed by some writers [0-3] The possibility of a conditioned deficiency must be taken into consideration It may be that coincidental riboflavin deficiency can aggravate rosacea keratitis, in which case benefit may be derived from riboflavin administration

Another condition associated with corneal vascularization is phlyctenular or eczematous kerato-conjunctivitis Here the situation is quite different this disease is actually nothing but a manifestation of true ariboflavinosis against an allergic background Patients suffering from it make a dramatic recovery with riboflavin by mouth without any local treatment while the usual treatment with yellow oxide of mercury atropine cod liver oil etc is in many cases a very tedious affair The condition occurs mainly in undernourished children who show stigmata of scrofulous diathesis The hypersensitivity of the conjunctival and corneal tissues is supposed to be caused by hidden, perhaps clinically healed tuberculous lesions provoked either by the tuberculous antigen or by other bacterial toxins (hetero allergy) But the actual manifestations of eczematous kerato-conjunctivitis with the appearance of corneal vascularization (eczematous pannus) and eczematous lesions of the face, are caused by riboflavin deficiency It is known that patients of the "scrofulous type frequently have a craving for carbohydrates and consume them in great quantities—a diet likely to lead to ariboflavinosis

Patients with eczematous kerato-conjunctivitis show very low riboflavin values in the urine [24] This together with the therapeutic effect of riboflavin certainly suggests that eczematous keratitis is a manifestation of ariboflavinosis, released by nonspecific stimuli of an allergic nature in predisposed individuals These nonspecific stimuli may be naso pharyngeal disorders infectious agents or even mechanical irritation Ariboflavinosis however, is always the essential basic condition The prompt therapeutic effect of cortisone in eczematous keratoconjunctivitis observed by Thygeson and Fritz [5] does not invalidate this contention Cortisone is a very effective agent in combating allergic manifestations of any kind by blocking the inflammatory reaction but it has no specific effect

Another disease characterized by corneal vascularization is trachoma Typical trachomatous pannus is limited to the upper part of the cornea and cannot be confused with ariboflavinotic vascularity There are cases however, in which a marked discrepancy exists between the appearance of the active pannus and that of the smooth and well-cicatrized palpebral

conjunctiva The patients complain of watering, itching, and burning, and sometimes even exhibit marked photophobia The palpebral conjunctiva is inactive and not amenable to treatment Nonspecific treatment with atropine, etc, alleviates the symptoms but cannot prevent relapses On careful examination with the slit lamp, the cornea is frequently found to be vascularized not only in its upper half or third, as in classical trachomatous pannus, but in its entire circumference, as in ariboflavinosis Treatment with riboflavin promptly relieves the condition [26] The therapeutic success in such "intractable" cases of trachomatous pannus means that they are provoked by ariboflavinosis, causing typical vascularization of the cornea The vessels of the trachomatous pannus never leave the cornea entirely but remain visible through the slit lamp as minute, empty channels If riboflavin deficiency occurs at this stage of trachoma, the well known response of the cornea sets in the limbic plexus becomes flushed, and newly-formed capillaries encroach upon the cornea In the upper half of the cornea, where the old channels of the trachomatous pannus are still present, there is no new formation of vessels, but the vessels of the pannus become engorged and present the picture of active trachomatous pannus Adequate provision of riboflavin will then, of course, exert its beneficial effect on the old pannus as well as on the newly formed vessels

Corneal vascularity of the same type as that found in ariboflavinosis occurs in rats on diets deficient in protein or in any of the essential amino acids It is probably due to some metabolic upset in the corneal cells caused by the absence of these substances A similar type of vascularization occurs in zinc deficiency,[27] sodium deficiency,[28] and thallium poisoning [29] Although this vascularity is of the same type as that in ariboflavinosis, it seems to occur only under experimental conditions unlikely to be encountered in clinical practice hence, it need rarely, if ever, be considered in the differential diagnosis

In the foregoing, an attempt has been made to arrive at an answer to the question of the specificity of corneal vascularization as a sign of ariboflavinosis We believe that vascularity of the type described is indeed a pathognomonic sign of riboflavin deficiency Another question arising in this connection is whether ariboflavinosis always causes corneal vascularization

It seems that a low intake of riboflavin must continue for a prolonged period of time before anatomical signs of the deficiency, and particularly corneal vascularization, make their appearance This is surprising in view of the fact that riboflavin is water-soluble and might be expected to be washed out of the organism in a short time in a deficiency state It can perhaps be explained by assuming that riboflavin is bound in the organism to the protein of enzymes and cells In rats on a riboflavin-deficient diet, the first signs of corneal vascularization appear only when the riboflavin concentration of the cornea falls to less than 50 per cent of normal In rats on a comparatively riboflavin-free diet, this stage is reached in three weeks but in animals on a diet containing only slightly less than the optimum, it takes a considerably longer period of time [19]

In deficiency conditions, biochemical changes and impairment of function usually precede morphological changes Corneal vascularity is a

relatively late result of functional disturbances and is an expression of a well established deficiency It represents the response of the organism to a degree of impairment of function that makes the continuation of normal metabolic processes impossible

A deficiency disease may be caused not primarily by an inadequate diet, but rather by interference with absorption or utilization of essential nutrients, or by increased requirements, destruction or excretion Jolliffe has termed these states "conditioned malnutrition,[30] and Kruse has given this concept an important place in the science of nutrition [31] Cases of corneal vascularity after surgical trauma to the cornea (corneal transplantation) are an example [32] Here, the trauma is to be regarded as the conditioning factor The healing process after trauma causes increased activity of the corneal epithelium and stroma with a correspondingly high oxygen requirement Thus, a degree of riboflavin deficiency which remains subclinical under normal conditions may lead to corneal vascularization when other pathologic conditions increase the corneal metabolism In experimental animals prolonged deprivation of riboflavin definitely handicaps the healing process of experimental corneal lesions [33] This then is the answer to the question as to why not every case of dietary riboflavin deficiency displays signs of corneal vascularity Unless the deficiency has reached considerable proportions or unless a conditioning factor comes into play corneal vascularity will fail to appear

Treatment —It seems obvious that a deficiency ought to be cured by the administration of sufficiently large doses of the lacking element The recommended dietary allowance for the human organism is about 1 5 to 2 5 mg riboflavin per day (more during pregnancy and lactation) Riboflavin is not stored in the organism to the same extent as are the fat-soluble vitamins no major depots are available in a deficiency state and the supplying of the normal demand should be sufficient to establish a well balanced function Empirically however, it has been found that it is advisable to give therapeutically at least 5 to 10 times the amount required physiologically This might be an indication that there *are* depots to be replenished—not depots of riboflavin as such but of riboflavin combined into the large molecules of enzymes and other proteins of which it is a component Faulty absorption of riboflavin in a disordered gastrointestinal tract is another possible explanation of riboflavin deficiency occurring despite a well balanced dietary regimen, and another indication for higher therapeutic requirements

Riboflavin occurs in nature together with all the other B-complex factors and a deficiency of riboflavin alone should really not be thought possible What happens is probably that a general deficiency of the vitamin B complex remains subliminal and that the first clinical sign to appear is the one due to a lack of riboflavin when the condition reaches pathogenic proportions Vascularity of the cornea can therefore be cured clinically with riboflavin alone, it is however safe to assume that the other B factors are also lacking to a certain degree and it would seem advisable to treat these cases not with riboflavin alone but with the whole vitamin B complex Vitamin therapy is at its best only a substitution therapy The cause for the deficiency has to be found be it dietary or organic and eliminated at

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its source It is probable that the greatest importance of vitamin deficiency in clinical medicine lies in border-line cases of ill-health which frequently puzzle the physician and disable the patient It is quite possible that in partial avitaminosis the *cumulative damage to the important epithelial structures of the eye may lower their vitality, favor the incidence* and prolong the activity of *infection*, and precipitate degenerative changes on a wider scale than is yet realized[34]

Acute Manifestations —In the preceding section, the ocular signs of ariboflavinosis were described as they occur in cases taking a more or less chronic course This is not always the case The condition can assume the aspect of a violent, acute disease[3 36] Such cases present very marked photophobia and intense hyperemia, mainly of the bulbar conjunctiva No mucous or purulent discharge is present, but lacrimation is profuse The *conjunctival smear is sterile or shows harmless saprophytes With the* slit lamp, the limbic plexus is seen to be maximally engorged The loops, transformed into tiny convolutions of capillaries, send out fine vessels 3, 4 or more millimeters into the subepithelial corneal layers The newly formed capillaries sometimes stand out plastically from the corneal epithelium The epithelium covering the vascularized part of the cornea is edematous and shows cyst-like vesicles filled with clear fluid These may break down *and produce small ulcers that stain with fluorescein*

Gross dietary deficiency can be found in the history and, in some cases, the condition is provoked by acute infections such as tonsillitis Mild signs of other deficiencies of the vitamin B complex are often observed such as pellagroid pigmentation of the skin and over active tendon reflexes These cases represent acute exacerbations of long-standing chronic deficiency states, provoked by a sudden deterioration of the general state of health Acute infectious diseases, gastro-intestinal *disorders or similar occurrences* will almost always be found in the history

The condition looks so alarming that hesitation may be felt about limiting therapy to riboflavin The prompt response of the eyes to this medication is however, most gratifying, and local treatment is generally superfluous

Amino Acid Deficiency

Etiology —Rats on a tryptophane-deficient diet which receive sufficient amounts of vitamin B complex develop vascularity of the cornea[7 38] Most of the other essential amino acids produce the same effect when absent from the diet of experimental animals leucine,[39 40] histidine,[3 41] lysine,[4] methionine[43 44] isoleucine[39] threonine, valine, arginine and phenylalanine[39 45]

Pathology —The ocular reaction to any of these deficiencies is a congestion of the scleral *conjunctiva* and *engorgement* of the limbic plexus, followed by slight thickening and diffuse corneal clouding, capillary 'sprouts shoot from the marginal limbic vessels and these new capillaries invade the clear cornea

This corneal vascularity resembles closely that observed in riboflavin deficiency however, deep vascularization and keratinization of the epithelium frequently distinguish it from ariboflavinotic vascularity This keratinization has been termed "nutritional corneal dystrophy"[40 41] It is

reversible if treated in time with the missing amino acid It is important to note that it does not respond to riboflavin administration Amino acid deficiency must therefore exert some direct effect upon the cornea, rather than acting by inducing a deficiency of riboflavin

Prevalence —In rats, general protein deficiency not only deficiency of a single amino acid may result in the appearance of corneal vessels In man however this has never been observed A clear-cut deficiency of a single amino acid is unlikely to occur clinically in man and it is doubtful whether it ought to be taken into consideration in the differential diagnosis of corneal vascularity This problem is however far from being settled Givner[46] has observed 2 cases of exfoliative dermatitis with corneal changes similar to those seen in experimental valine deficiency Administration of amino acids parenterally and aminoids and protein by mouth was followed by clearing of the cornea and finally by complete recovery

Local Application —Amino acids have been applied externally to one experimentally injured cornea of guinea pigs while the other cornea with a similar injury was treated with isotonic saline as control Regeneration of the cornea in the eye treated with amino acids was much more rapid[47]

Angular Blepharo Conjunctivitis

Pyridoxine (vit B_6) has been shown to be a factor in angular blepharoconjunctivitis Patients with this condition have a low pyridoxine level in the urine and the causative organism hemophilus duplex (Morax Axenfeld bacillus) survives longer in the conjunctiva of pyridoxine deficient rabbits than in normal controls[47a] While the condition is doubtless of bacterial origin pyridoxine deficiency seems to play a role in its establishment and it can be cured by pyridoxine without any local therapy[47b, 47c]

Keratoconus

The etiology of keratoconus is not established It has been shown that lack of vitamin E in the diet of rats occasionally causes keratoconus as well as other ocular disturbances they could be cured by administering the missing vitamin Progressive cases of keratoconus in man have been treated with some benefit with vitamins E D and calcium[48–51] The results however have not been confirmed

Interstitial Keratitis

Vitamin E was found to be beneficial in syphilitic interstitial keratitis[52] It hastened absorption of superficial and deep corneal exudates thus preventing scar formation The addition of riboflavin appeared to have some effect on the corneal vascularity rapidly improving interstitial syphilitic keratitis[53] Anti syphilitic treatment was of course also given It is possible that there was an associated severe ariboflavinosis or that riboflavin deficiency released the pathogenetic mechanism of parenchymatous keratitis (conditioned deficiency)

Spring Catarrh

Riboflavin and nicotinamide alleviate the subjective complaints of patients with spring catarrh, without, however, appreciably influencing the anatomical changes[54, 55] Spring catarrh undoubtedly is an allergic condition

Calcium ion has also been used widely in the treatment of spring catarrh It is believed to exert a sealing action on the conjunctival capillaries

Vitamin Treatment of a Variety of Corneal Diseases

Riboflavin —Certain corneal diseases, such as superficial punctate keratitis, corneal ulcer, catarrhal infiltrates, etc, have occasionally been reported to be favorably influenced by riboflavin[56–58] It is not unreasonable to assume that riboflavin has an unspecific pharmacodynamic effect on a multitude of corneal diseases Moreover, a number of corneal diseases the *etiology of which is not known may, sooner or later, reveal themselves to be* due to a disturbance of riboflavin metabolism

Thiamine —Favorable results *have been claimed for thiamine therapy* of herpetic infections of the eye, like herpetic keratitis, disciform keratitis punctate keratitis and ophthalmic herpes[59–6] The rationale of this therapy might be similar to that of riboflavin

Vitamin C —Corneal inflammations like superficial keratitis, chronic infiltrates, and ulcers have been reported to improve strikingly on oral vitamin C therapy[63] It has also been claimed that the addition of vitamin C to the routine treatment of hypopyon ulcers made the hypopyon disappear more rapidly[64]

The cornea of rabbits has a selective absorptive power *for vitamin C*, which penetrates into the aqueous humor through the healthy cornea That *vitamin C may be of importance for the cornea* is suggested by the observation that the vitamin C content of the cornea increases in rats suffering from keratomalacia due to vitamin A deficiency[65] Vitamin C is also necessary for the formation of collagen in the cornea[66] In scorbutic animals, thermal injuries to the cornea are followed by corneal vascularization at a significantly higher rate than in controls It can be assumed that the accumulation of metabolites leads to edema and opening of the corneal lamellæ which permits the blood vessels to approach the injured parts of the cornea[67]

LENS AND AQUEOUS HUMOR

Vitamin C in Ocular Biology

Presence of Vitamin C in Lens and Aqueous Humor —*The crystalline* lens occupies a unique place in physiology Devoid of nerves and vascular supply, it is freely suspended *in the aqueous humor* on which it depends for its nutrition It represents an isolated metabolic system, the respiratory *processes of which are mediated by* a system of relatively simple chemical compounds, these are able to transport hydrogen and oxygen and thus maintain oxidation and reduction activities They have been called redox

substances Sulfhydryl compounds like glutathione and cystine are known to play a role in these processes In 1932, Muller[68] reported that ascorbic acid in the lens is responsible for reversible oxidation-reduction processes Quantitative analysis brought out the fact that the amount of ascorbic acid in the lens and the aqueous was 10 or 20 times higher than in any other part of the body, except the adrenals the sex glands, and the hypophysis

The Function of Vitamin C in the Eye —The function of vitamin C in the crystalline lens and its surrounding fluid seems to be the mediation—together with glutathione and cystine—of the oxygen uptake of the lens All oxidation catalysts work best only at a potential very near to that of the system to be catalyzed The intermediary catalysts of the lens (ascorbic acid, glutathione, and cystine) probably have the task of bringing the potential of the oxidation substrate successively nearer to the last oxygen donator

Source of Vitamin C in the Eye —There are two possible sources of vitamin C in the eye (1) It may be brought to the eye by the circulation and accumulated by the lens and the aqueous (2) It may be formed in the lens and retained there and in the anterior chamber

The lens of the ox is capable of synthesizing ascorbic acid [69] A reaction which has been shown to occur *in vitro* may also occur in the living eye the conversion of lactose into ascorbic acid by cystine which is present in the lens in considerable quantities dextrose can also be converted by glutathione into ascorbic acid This formation of ascorbic acid is probably combined with a process of phosphorylation Intravenous injection of glucose is likewise followed by a rise of the ascorbic acid content in the aqueous, suggesting a similar process [70]

Further proof that at least part of the ascorbic acid in the aqueous is produced by the lens is the fact that the high vitamin C content of the aqueous in man is maintained only when the lens is present and intact In cataract and aphakia the percentage of ascorbic acid in the aqueous falls almost to its level in the blood [71] When the lens is intact, ascorbic acid in the aqueous is present in an oxidized form in eyes with cataract it is found in a reversibly reduced form [72] Ascorbic acid is brought into the anterior chamber where in the presence of a healthy lens it becomes converted by dehydrogenation into the oxidized form thus playing a part in the oxidation reduction system of the lens

The blood aqueous barrier is usually permeable to reversibly oxidized ascorbic acid in the direction blood→aqueous while it is impermeable in the opposite direction The high content of ascorbic acid of the aqueous is therefore caused at least partly by the following mechanism (1) supply of oxidized ascorbic acid from the blood (2) reduction of ascorbic acid by the lens (3) retention of the reduced ascorbic acid by the blood-aqueous barrier

Vitamin C in Ocular Pathology —Vitamin C plays an important role in the respiratory processes of the lens In pathologic conditions these processes are altered and the vitamin C metabolism reflects this disturbance As the lens ages, its respiration becomes less intense and the lens nucleus contains less vitamin C than the biologically more active cortex If the respiratory processes of the lens are suppressed by cataract or absence of

mechanisms are generally accepted as responsible for the production of cataract one is the decrease in the permeability of the lens capsule in the presence of glucose and ketone bodies, the other is the disturbance of the tissue-fluid equilibrium causing, by osmotic influences, hydration of the lens

The occurrence of senile cataract depends less upon the severity of the diabetes than upon the duration of the disease However, true diabetic cataract in young persons—and even children—is usually encountered in the more severe cases in which maintenance of a good water balance is still possible

Treatment —Treatment of early true diabetic cataract can be quite effective if it is started before denaturation of the proteins in the lens has set in and only edema is present Adequate control of the diabetes can then result in complete disappearance of the lens opacities

Presenile cataract in older diabetics does not respond to medical treatment Surgery must be resorted to sooner or later, and, while complications must be feared more than in non-diabetics, the disease itself is no contraindication

Galactosemia and Cataract —Galactosemia is a congenital and hereditary error of carbohydrate metabolism The usual symptoms, occurring within a few days after birth, consist of vomiting, lethargy, fever and failure to gain weight The clinical signs include jaundice, ascites, hepatomegaly and splenomegaly Bruch and Rapoport[84] published in 1943 a very interesting case of galactosemia causing cataracts, and the occurrence of this ocular complication has been reported with increasing frequency Galactosemia is due to the absence of a specific enzyme necessary for the utilization of galactose This leads to an accumulation of an intermediary metabolic product, galactose-1-phosphate,[85] which probably has a toxic effect on such tissues as liver spleen, brain and crystalline lens Treatment consists in withdrawing milk and instituting galactose- and lactose-free diets which usually lead to rapid recovery and prevention of cataracts

Transitory Changes of Refraction in Diabetes

Transitory changes of refraction in diabetes are not uncommon The sudden onset of myopia (or reduction of hypermetropia) indicates the rapid rise of the blood sugar concentration, in a previously healthy adult diabetes is to be suspected and in a known diabetic it points to improper control of the disorder Sudden hypermetropia, on the other hand, occurs if diabetes is treated too rigorously and the blood sugar is lowered too rapidly According to Adler[86] diabetogenic changes of refraction occur because of a difference of sugar concentration in aqueous and vitreous, alone or together with changes in the lens

RETINA, OPTIC NERVE AND VISUAL DISTURBANCE

Night Blindness

Signs and Symptoms —One of the first symptoms of vitamin A deficiency is night blindness Unfortunately, two diametrically opposed

terms—etymologically—are used for this condition, hemeralopia and nyctalopia, however, the term night blindness is expressive, unequivocal and should be used

Vitamin A deficiency is only one of the several causes of night blindness It occurs in all conditions that prevent the rods, cones or both from participating to their full capacity in the visual process conditions in which retinal disease has resulted in destruction or dysfunction of the nervous elements The adaptation curve will become abnormal according to the kind of elements most affected—rods or cones—and the degree of impairment The rods are the elements responsible for light discrimination in reduced illumination and, while the function of the cones is also affected in vitamin A deficiency, it has been established that for practical purposes the best single criterion is the final rod threshold Deterioration of dark adaptation is also accompanied by changes in the color sensitivity of the retina The fields for blue and red may become diminished or even inverted, and a shrinking of the field for yellow may be observed Concentric constriction of the visual fields may occur, a sign probably indicating involvement of the cones as well as of the rods

The role of vitamin A in the visual process has been the subject of intense study since Wald[87–89] demonstrated that it is an essential constituent of visual purple Visual purple is a heavy protein molecule with vitamin A as a prosthetic group This compound also called rhodopsin, exists in the dark adapted retina and is transformed by light into visual yellow, unlike visual purple this is not a compound but a mixture of a protein and carotenoid substance called retinene On steady exposure to light, visual yellow changes into visual white a mixture of vitamin A and a protein On staying in the dark vitamin A disappears and visual purple is re-formed

The change of visual purple into visual white and its reconversion into visual purple is associated with a loss of vitamin A which must be replenished from dietary sources

The reason for a vitamin A deficiency may be twofold either inadequate intake of the provitamin or the vitamin from vegetable or animal sources, or else a disturbance of the process of synthesis of vitamin A in the human organism due to gastro-intestinal or liver disease The role of liver disease in the etiology of night blindness is demonstrated by the fact that dark adaption is frequently disturbed in cirrhosis of the liver hepatitis etc [90] There is a significant relationship between other nutritional deficiencies and impaired dark adaptation Riboflavin[91, 9] thiamine [93] and nicotinic acid amide[94] have been reported to be effective in alleviating night blindness and other vitamin A deficiency signs when vitamin A alone failed to bring on recovery The vitamin B complex may thus play a role in the utilization of vitamin A Another possible relationship is suggested by reports of a beneficial effect of ascorbic acid on night blindness [95, 96] Certain amino acids, chiefly l glutamic acid and l-cysteine have also been shown to improve the curve and the threshold of dark adaptation [97]

The conversion of the carotenoid retinene into vitamin A is effected by an enzyme system which has been isolated Retinene is vitamin A aldehyde vitamin A a primary alcohol For the reduction of retinene to vitamin A the retina contains an enzyme—retinene reductase and a co-enzyme

—reduced co-zymase This latter substance has nicotinamide as its central component

Failure of conversion of carotene into vitamin A explains the occurrence of xerophthalmia in severe hepatic insufficiency and intestinal disturbances Generally, disease and old age can apparently diminish the capacity of the organism to transform carotene into vitamin A In these cases carotene may fail, while vitamin A cures the symptoms of the deficiency Age seems to play a physiologic part in dark adaptation, and a progressive deterioration of this capacity has been charted, amounting to about 0 12 log units for an increase of ten years [98]

Considerable difficulty was experienced in the attempt to establish experimentally the period of reduced vitamin A intake required to cause disturbances of the light sense Several factors have to be taken into consideration The most important one seems to be the storage of vitamin A in the liver As long as this was disregarded in experiments, the results were unreliable Many persons respond to an experimental vitamin A deficiency with a prompt rise of the rod threshold, while in others it takes weeks or months before deviations of the normal adaptation curve can be observed The latter response seems to be the more frequent one

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Severe vitamin A deficiency is, however rare in Western countries Yet it is believed that the great majority of Americans in the lower income groups are not receiving enough vitamin A to assure normal dark adaptation In Britain it has been shown[103] that, of those school children who received two thirds of a pint of milk a day in school, 67 per cent had normal dark adaptation while only 37 per cent of others receiving only one-third of a pint of milk or less daily showed normal dark adaptation curves Measurements of dark adaptation may be used to assess nutritional levels in respect to vitamin A either by the determination of the effect of vitamin A on dark adaptation, or by the comparison of the values of dark adaptation in various groups The latter method, while not providing such conclusive evidence as the former may sometimes provide presumptive evidence of the relative nutritional status in respect to vitamin A and for technical reasons it may be the only feasible procedure [104]

Differential Diagnosis—There can be no doubt that wide physiologic variations in the light sense occur, there are individuals with a normal level of vitamin A in the plasma who have a physiologically low sense of light which cannot be improved with vitamin A Moreover, psychic factors age, fatigue, depression, or ocular lesions all play a part Derangements in the light sense cannot, therefore be used as an exclusive test for vitamin A deficiency chemical estimations of vitamin A in the blood are necessary Only when the vitamin A concentration falls below a certain limit is there a measurable deficiency in the sense of light Subjective night vision disturbances, however, begin only with a much lower vitamin level

With normal blood values the light sense is usually good Of subjects with normal average values of light sense a rather small percentage improves on vitamin A therapy These individuals have probably an exceptionally good light sense and happen to suffer from a very slight degree of avitaminosis A, there is nothing to suggest that hypervitaminosis increases the light sensitivity

Treatment—It seems that recovery from disturbances of dark adaptation is relatively slow Short term therapy with high doses of vitamin A has only a slight effect and is followed, at best, by a transitory, incomplete recovery Complete recovery is a matter of weeks and months This slow recovery rate indicates some deep seated lesion, the development of which may be peculiarly favored by the sudden and acute onset in experimental depletion of vitamin A, the long continuance of a deficiency diet, and also, perhaps, by the sharp restriction of vitamin A alone

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retinal disturbances are a measure of the therapeutic success, and considerable improvement can be observed true, it is only temporary, but it might prevent permanent damage until other therapeutic measures are able to regulate the cardiovascular complications [113]

It is interesting that the intra ocular tension in normal eyes has been observed to fall as soon as a rice diet is introduced The relative depletion of chlorine and sodium ions in the tissues might be responsible for this

Nutritional Amblyopia

During and after World War II numerous cases of serious neurologic and metabolic disturbances were seen among prisoners of war and internee camp inmates They nearly always showed ocular changes The greatest number of serious cases were observed in the unfortunate victims of the Japanese prison camps but less severe cases were also described in others In retrospect these cases are clinically comparable to those observed earlier in the malnourished population of tropical countries

Early Japanese writings on beriberi indicate that retrobulbar neuritis scotomata, and oculomotor palsies have been encountered with varying frequency in oriental beriberi Involvement of the optic nerve with pallor of the nerve head and relative central scotomata have also been described in pellagra Vitamin B complex has a beneficial effect on such cases

Retrobulbar neuritis is a not uncommon effect of malnutrition in tropical countries and vitamin B complex has often been reported as being beneficial in its treatment Progressive loss of vision with temporal pallor of the optic disc as seen in India frequently responds to vitamin A therapy [114]

Visual disturbances in prisoners of war were characterized by a retrobulbar neuritis, when it existed for any length of time permanent damage to the optic nerve resulted The highly sensitive papillo-macular bundle, in particular suffered to a marked degree

The majority of observers accept a serious deficiency of the vitamin B complex as the etiologic factor in this condition Protein deficiency a hypothetical toxin from mouldy rice and general malnutrition probably contribute to its development

The mottling of the macular retina in nutritional amblyopia is similar in appearance to the fundus changes of solar retinopathy occurring in people who observe a solar eclipse without adequate protection the retinal damage of nutritional amblyopia may be attributable to the action of the tropical sun upon a tissue that has become sensitized to light by a dietary deficiency as in pellagra, or beriberi

Toxic Amblyopia —The nutritional amblyopia in the tropics and among prisoners of war seems to be closely related to the retrobulbar neuritis—toxic amblyopia due to alcohol and nicotine Toxic amblyopia is considered to be the result of a toxic action of nicotine and alcohol on poorly nourished nerve cells It is possible to cure toxic amblyopia by placing the patient on an adequate diet or by giving him thiamine even without depriving him of the habitual intake of alcohol or the use of tobacco This points to thiamine deficiency as being a factor in the pathogenesis of toxic retrobulbar neuritis Evidence also has been presented that the retina or

under the influence of light This property is typical of riboflavin and it is reasonable to assume that this vitamin exists in the retina It has been suggested that riboflavin has a special function during twilight, transforming light of short wave length into light of a wave frequency for which the eye has a maximum sensitivity [105] This postulate can be upheld by certain clinical observations Cases have been described of impaired night vision and reduced vitamin A level in the blood which failed to respond to vitamin A, but reacted with both improved night vision and raised vitamin A plasma levels when riboflavin was administered [106–109] These observations suggest that riboflavin plays a part in the utilization of vitamin A

Diabetic Retinopathy

There is some evidence that nutritional imbalance plays a part in the pathogenesis of diabetic retinopathy The oxygen consumption of the isolated retina of alloxan-diabetic rabbits is significantly lowered,[110] and the same fact has been observed in experimental thiamine deficiency,[111] improper diet and B-complex avitaminosis have been accused of being partly responsible for the typical retinal involvement, with hemorrhages and exudates

A frequent finding in poorly-treated diabetics with retinopathy is an abnormal plasma protein level The total quantity may be slightly reduced or normal, but albumin is found to be reduced and beta globulin increased While adequate treatment with a high protein diet may restore the normal balance between the protein fractions in most cases, the retinal condition responds only in a certain percentage however, improvement in the retinopathy can be expected only if one succeeds in normalizing the abnormal distribution pattern of the blood proteins

It must be mentioned also that diabetic patients have been found to have levels of carotene and vitamin A outside the range established for healthy persons Thiamine is considerably reduced in the blood and the gastric juice of diabetics and it has been stated that this vitamin enhances the effect of small insulin doses decreases the blood sugar of normal dogs, and depresses the blood sugar curve in dogs after glucose intake [11] It increases the glucose tolerance of diabetics in about 50 per cent of the cases

Some of these statements need confirmation Diabetic retinopathy has come under particularly close scrutiny lately, and there are certainly other factors involved, more important than the nutritional ones enumerated above But there can be no doubt that experimental diabetes is increased in severity by deficiencies of the vitamin B complex and that diabetics with concomitant vitamin deficiency symptoms respond to vitamin therapy with amelioration of the severity of their diabetes and its retinal manifestations

Rice Diet —The use of the rice diet in hypertensive disease has been discussed fully (see p 721) Brief mention must be made here of its beneficial effect on the ocular manifestations of severe hypertension—hemorrhages, exudates and papilledema It seems that these vascular complications in the eye can be influenced favorably by strict adherence to the rice diet If sufficient cooperation can be obtained, the receding

tissue Optic nerve degenerations were also observed in rats on a diet deficient in vitamin A[125] and much more severe changes occurred when the avitaminotic animals were exposed to various poisons and bacterial toxins[126]

Prevalence —It is to be borne in mind that the experimental results were obtained in animals exposed to an extremely vitamin A-deficient diet Vitamin A-deficient animals whose litters were born with malformations of the eyes had vitamin A serum levels of one tenth or less of the normal Such extremely low levels are not likely to occur in man

Myopia

Convincing experimental and clinical evidence has been presented that the animal protein content of the diet can influence the state of refraction in the growing animal[126a] and child[1 65] A group of nearsighted children received, in a carefully conducted controlled study extra animal protein the rate of increase in myopia was much less than in a control group whose diet was not changed While other factors must be at work as well the course of myopia in children and adolescents can be beneficially modified by dietary means

Wernicke's Syndrome

In Wernicke's syndrome an ophthalmoplegia is observed associated with clouding of consciousness ataxia and other manifestations of central nervous system involvement The basic pathology of this syndrome consists of small foci of degeneration varicose blood vessels, and petechial hemorrhages in the cerebral cortex and the region of the nuclei of the third fourth and sixth cranial nerves The etiology of the syndrome is complex, but thiamine deficiency seems to be the cause of the ophthalmoplegia, and thiamine administration may cure it promptly[127–131]

Central Nervous System

It has been stressed in this chapter that subclinical nutritional disorders may be responsible for disturbances of the visual apparatus that subclinical vitamin deficiencies may predispose the eye to the action of endogenous or exogenous toxic influences and vice versa It is apparent that the establishment of an adequate nutritional environment is essential for the maintenance of optimal performance of all vital functions In addition to the clear-cut deficiency states, however there are many degenerative diseases of the vascular system and metabolic disorders which affect the nutrition of the eye and its nervous centers causing visual disturbances

Central nervous system fatigue is the most common and most important type of fatigue encountered in modern industry[132] Disturbances of vision may be the earliest detectable sign of such fatigue The power of accommodation seems to suffer in thiamine malnutrition and the administration of this vitamin or vitamin B complex is beneficial in many cases This is understandable in the light of Sysi s investigations who found that even

the optic nerve is unduly sensitive to tobacco in even mild vitamin B_{12} deficiency. Amblyopia may precede other manifestations of the deficiency, and parenteral administration of cyanocobalamin improves visual acuity and reverses the field changes.[135a] Vitamin B_{12} has been used successfully in other optic nerve diseases.[135b]

While the ultimate goal in the treatment of these patients is, of course, to discontinue completely the abuse of alcohol and tobacco, serious nervous complications can be prevented by the prompt institution of adequate dietary and vitamin therapy.

Vitamin B complex and thiamine have also been used at times with good results in the treatment of retrobulbar neuritis of unknown origin, however, the role of thiamine in these conditions is not very well understood.

Another instance of a conditioned affection of the optic nerve is the retrobulbar neuritis occasionally encountered in pregnancy. The increased vitamin requirement in pregnancy and hyperemesis gravidarum, impairing vitamin intake, are probably the conditioning factors. Thiamine has been used with benefit in retrobulbar neuritis of pregnancy. The same may be true for the rare cases of retrobulbar neuritis following unduly prolonged breast feeding without adequate replenishing of the vitamin stores of the mother. According to Moore and Woods,[136] vitamin A deficiency plays a definite role in the pathogenesis of syphilitic optic nerve atrophy, and this seems to be another example of an affection conditioned by vitamin deficiency. In this connection, it may be interesting to mention the observation of a severe avitaminosis A in a case of syphilitic diffuse hepatitis with hypoplasia of the Kupffer system and very little vitamin A in the liver.[115]

Pathology.—There is scanty information available concerning the anatomical changes in the optic nerve of thiamine-deficient animals. Cocarboxylase is the di-phosphoric acid ester of thiamine. This co-enzyme is important in the oxidation of pyruvic acid in the nerve tissue. In thiamine deficiency, therefore functional and anatomical manifestations may result. There is no proof, however, that the damage is really due to any toxic action of pyruvic acid. The optic nerve of thiamine-deficient pigeons with beriberi shows edema and interruptions of the myelin sheath.[116] Degeneration of the myelin sheath manifests itself by the formation of lipoid granules particularly in the papillo-macular bundle.[117]

The effect of vitamin A deficiency on the peripheral nerves (trigeminal) has been mentioned in the discussion of xerophthalmia. The first evidence that vitamin A is necessary for normal functioning of the nerve tissue was offered by the finding of severe degenerative changes in the optic, sciatic, and femoral nerves of young pigs fed on a vitamin A-deficient diet from the time of weaning.[118] Pigs, calves, or rats whose mothers are fed a diet deficient in vitamin A are born with anophthalmos or microphthalmos.[119,120] These conditions are attributed to a malformation of the optic nerve, either primary or due to a stenosis of the optic canal.[121–123] Young dogs fed a diet deficient in vitamin A develop degeneration of the spinal cord, the eighth nerve and also the optic nerve.[124] In one animal maintained on such a diet for seven years, the ganglion cell layer of the retina had completely disappeared and the optic nerve was replaced by a strand of connective

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normal, healthy subjects experience an increase in the power of accommodation after the injection of 25 to 100 mg thiamine [133] Thiamine affects the amplitude of accommodation by increasing its capacity beyond normal limits, through its action on the ciliary neuro-muscular mechanism [134]

Similarly, the fusion frequency of flicker (the frequency at which successive light flashes produce the impression of plain light instead of flicker), is disturbed in nervous fatigue and can be improved by thiamine administration [134]

Much critical work is required to clear up the important and largely unknown relations between malnutrition and the functions of the central nervous system In using fusion frequency of flicker and the power of accommodation as objective tests for fatigue one may be in a position to make practical studies on the relation of nutritional status to resistance to, and recovery from, fatigue

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Chapter 34

Nutrition in Pregnancy

By Robert W Hillman

Gestation is the epitome of purposeful growth As a physiological process with pathological potential, pregnancy represents a period of particular stress The inordinate increase in fetal, sustaining and even non reproductive maternal tissues is characterized by equally unique nutritional requirements Optimal development of the infant—"nutritionally nine months old at birth"—is necessarily a function of maternal diet, before as well as during pregnancy Similarly, the mother s nutrition is important to the total well being of both parent and child long beyond the neonatal period

The special nutritional demands imposed on the maternal organism throughout the "reproductive interlude are attested by extensive clinical and laboratory observations Livestock studies, beyond an abundance of animal protein for the prospective mother, have contributed pertinent knowledge concerning, in particular, mineral metabolism during pregnancy and lactation Long term observations in sheep have especially furthered understanding of calcium utilization and of the roles of copper, cobalt and other trace elements during gestation [1]

Laboratory animal studies probably have been less directly applicable to human experience They have, however, identified possible genetetic needs in reproduction, for both protein factors and specific micronutrients The experimental production of congenital anomalies notably by Warkany,[2] has emphasized the importance of timing dosage and duration in the utilization of dietary components An excess as well as a deficit of a required substance evidently conduces to a variety of detrimental effects, ranging from neonatal death through successively earlier gestational adversities to actual failure of conception The complex pathogenesis of these abnormal events is suggested by similarity to genic effects, as well as to those induced by numerous physical and chemical agents—presumably through common enzyme deficiencies and anoxia of the critically sensitive differentiating tissues Species differences as well as the fundamental biological interdependence of all nutrients obviously limit application of these studies to man

Clinical observations predominantly support the concept of a relationship between maternal nutrition and the outcome of pregnancy Overall evaluation is complicated by both difficulties in diagnosis particularly of functional disorders, and the need to reconcile often conflicting results —fetal as opposed to maternal early as opposed to late effects The distinct yet inseparable metabolic entities represented by the fetus, mother and

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Current thinking on antenatal (and prematernal) nutrition is influenced increasingly by the extensive, not completely reconcilable, observations of two groups of investigators Tompkins, Wiehl and their associates at the

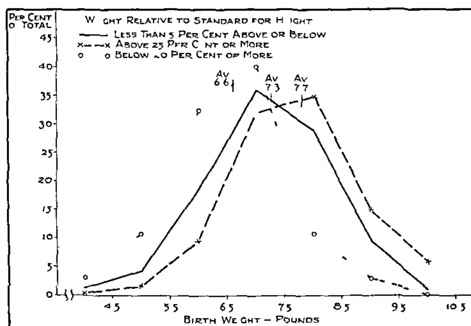


Fig 67 —Birth weight of babies born to mothers classified by weight at beginning of pregnancy

Lying In Hospital in Philadelphia[41] have presented massive evidence for the importance of maternal nutrition to the outcome of pregnancy The equally impressive investigations of Darby McGanity and their colleagues at Vanderbilt University[4] have not supported the importance of maternal diet on perinatal events

OBSERVATIONS AT THE PHILADELPHIA LYING-IN HOSPITAL

In general the studies of the Philadelphia group indicated significant relationships between the maternal weight pattern and (a) infant birth weight and (b) the occurrence of both toxemia and prematurity

Birth Weight —*Infant birth weight varied directly with weight at conception*—a strong association that operated independent of prenatal gain However, prenatal gain notwithstanding a negative relationship to pre-

the "placental barrier," comprise a complex nutritional system conducing to neither constant nor consistent performance In general, however relatively favorable results for both parent and progeny are noted in better nourished persons The principal parameters in respect to which the beneficial influence of good maternal nutriture appear manifest include frequency of toxemia and other maternal complications, length of labor, newborn weight (notably of the liver), height and chest circumference, the occurrence of prematurity, immaturity, abortion, sterility, and even intelligence of offspring

NUTRITION AND HUMAN PREGNANCY

Specific evidence for the importance of maternal nutrition to the outcome of pregnancy in man is derived from three general categories of observation (1) records of large population groups (vital statistics) with varying socioeconomic and health, including nutritional, status, (2) data for supervised hospital and clinic groups, and (3) controlled studies of patients receiving prescribed diets and/or nutritional supplements Much of this and other pertinent information has been reviewed by Garry and Wood (1946),[3] Stuart and Burke (1951)[4] and by Josey (1954) [5]

Population studies relating to maternal nutriture have originated principally in the United Kingdom, where, during World War II, overall *improvement in diet was associated with improved perinatal statistics* often despite otherwise unfavorable socioeconomic conditions (Sutherland [6] Baird,[7] Moncrieff[8]) Numerous for the most part smaller and better controlled studies have supported the impression of benefits attributable to good maternal nutriture in that country (Balfour,[9] Thomson,[10] Thomson, Graham and Billewicz [10] Cameron and Graham[11] The Peoples League[1]) Toverud in Norway,[13] *Riquelme and Alvorado in Chile,[14] Dean in Germany,[15]* Antonev in the Soviet Union,[16] Berry in Africa,[17] Hamlin in Australia [18] and Ebbs Tisdall and Scott in Canada[19] have reached similar conclusions In this country Stuart, Kirkland, Beal, Burke[4] [*0] and their associates have provided major support for good dietary practices during pregnancy Jeans Smith and Stearns [1] Ferguson and Hinson, [2] Brantley, [3] Block *et al*, [4] and Harrell Woodward and Gates[25] have reported corroborative findings

Complementary, if limited and indirect evidence has been provided by analyses of the effects of body weight on maternal experience Studies by Williams [6] Widdowson,[7] Beilly and Kurland [29] Douglas and Scadron,[29] Fisher and Fry [30] McKeown and Record,[31] and by Kerr[3] have indicated a positive relation between maternal weight and fetal size with large infants seemingly associated with parental obesity In this connection Baumgartner *et al*[33] showed that babies with birth weights 1 to 2 pounds above average (postmature) fared as poorly as infants of the same degree of underweight at birth Thomson and Billewicz[10b] has appropriately stressed the *quality* of babies which is just as variable as size and 'probably of more practical importantance " Borquin and Benum[34] observed that women with better nutriture responded more favorably to treatment for recurrent abortion

More equivocal and/or negative impressions concerning the influence of maternal nutrition on results of gestation have been forthcoming from

several sources, including Smith,[35] Williams and Fralin,[36] Speert, Graff and Graff[37] Dieckmann,[38] Petry,[39] and Scrimshaw[40] In these instances other conditions affecting perinatal morbidity may have been operative to a degree that claims for the specific role of nutrition could not always be substantiated—illustrating the difficulty of evaluating effects of a single variable where it is not necessarily the limiting factor, or where many other factors cannot be adequately controlled

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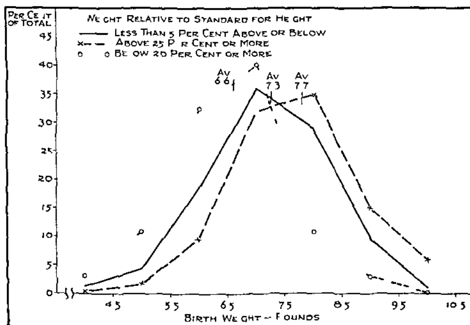


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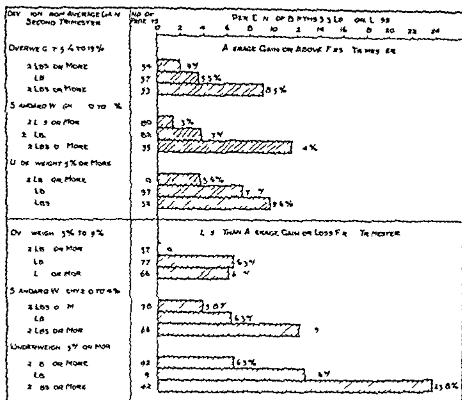


Fig 68 —Premature births according to gain in weight during first and during second trimester for patients of different pregravid weight

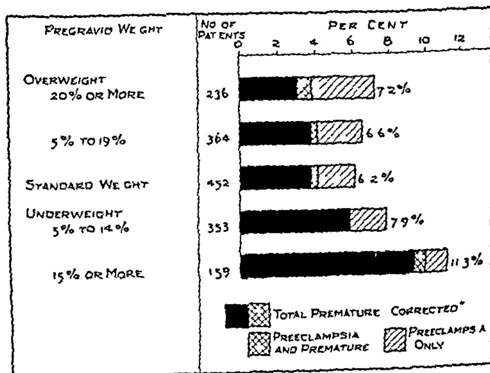


Fig 69 —Premature births and preeclampsia among patients classified by pregravid weight

gravid weight, also exerted some—albeit a lesser—effect on the baby. Among *overweight* patients, unrestricted weight gain did increase the chances of a very large infant (Fig 67). Among *underweight* patients failure to gain an average amount of weight tended to keep the baby small or to result in premature labor, but greater gain had little if any protective effect on the size of the infant. Premature separation of the placenta also occurred more frequently in these patients. Differences noted in the weight of infants born to underweight mothers were attributable to differences in birth length rather than to variations in soft tissue components relative to body size.

Prematurity.—The increased tendency to prematurity among patients underweight at conception was increased by inadequate weight gain during the first two trimesters of pregnancy. Moreover, even when the weight increment was average or above during the first trimester, failure to gain

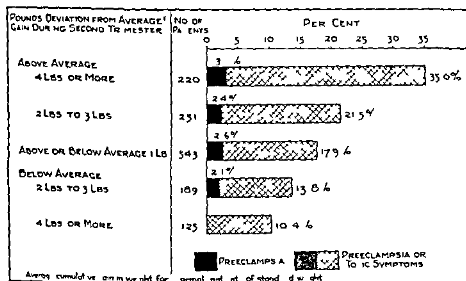


Fig 70.—Preeclampsia and toxic symptoms according to gain in weight during the second trimester. (Patients 20% or more overweight are excluded.)

in the second trimester markedly increased the probability of premature birth. (This pattern applied approximately equally to all weight categories.) Despite a satisfactory gain during the second trimester, a less than average increase during the first period nearly doubled the probability of premature birth. Protein and vitamin supplementation appeared to reduce the frequency of prematurity, except in patients over thirty, whose seemingly smaller margin of safety reflected more extended deprivation (Figs 68 and 69).

Toxemia.—Toxemia of pregnancy was more frequent among individuals definitely overweight at conception and among those gaining excessively during gestation—especially in the last two trimesters. Underweight patients were also more susceptible, with a rate many times that among standard weight subjects. Toxemia was sometimes superimposed on prematurity, but evidently was not an inherent part of this pattern. However, it was emphasized that "the individual who is underweight at conception is the greatest obstetrical hazard, having the greatest probability of both toxemia and premature labor." (Fig 70)

The incidence of toxemia among standard and overweight patients was apparently double that for the underweight group, whereas the incidence of prematurity among standard and overweight patients was less than half that of underweight gravida. Unlike normal weight patients, overweight pregnant women, usually with *more severe toxemia, were not protected* against this complication by failure to gain during the second and third trimesters. Comparable to those with above average gains, overweight patients with appreciably less than average increments also showed a greater frequency of toxemia than those showing an average increase. Protein and vitamin supplements appeared to reduce the frequency of toxemia, and also to conduce to delivery close to the optimum date of confinement, chiefly through reduction of early births. Nutrition supplements did not induce overall excessive weight gain as calculated from postgravid measurements (Fig 71 and Table 143).

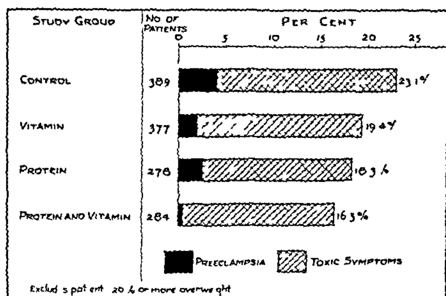


Fig 71 —Toxemia and toxic symptoms among patients in each study group

Laboratory Observations —The Tompkins' group also found the outcome of gestation to be related to the serum protein levels. In general toxemia occurred more frequently when total serum proteins were low—especially when the albumin fraction was also depressed. A low serum albumin in the absence of low total serum proteins was associated with a smaller incidence of toxemia while normal levels of both total protein and serum albumin were identified with the lowest frequency of this complication. An elevation in serum globulin appeared to protect in part against the effects of a reduced serum albumin. Factors other than protein consumption *per se* seemed also to be involved, a fall in serum proteins despite a satisfactory intake, was associated with a high incidence of toxemia. Considerable variation was noted in what seemed an inconstant relationship, subject to influences independent of diet.

OBSERVATIONS AT THE VANDERBILT HOSPITALS

The findings of the Philadelphia investigators have not been wholly corroborated at Vanderbilt. Darby and his associates concluded that their data have "failed to indict nutrition as a major causation in the development of commonly encountered obstetric and fetal abnormalities." Although the recorded experiences of the two groups have been comparable in many respects, significant differences have been evidenced in results and, particularly, in interpretation. In the Vanderbilt series underweight patients tended to consume more and overweight patients less food during pregnancy, but excessive weight gain was observed among patients in both of these as well as in the normal weight group. Although underweight patients tended to have more premature infants, this was in accord with the linear relationship between the mother's usual weight and the birth weight of the baby. Moreover, those mothers had fewer neonatal deaths and congenitally deformed infants.

TABLE 143.—PER CENT OF PATIENTS HAVING TOXIC SYMPTOMS THAT DEVELOPED PREECLAMPSIA CLASSIFIED BY STUDY GROUP AND PREGRAVID WEIGHT
(From Philadelphia Lying In Hospital)

Pregravid weight and study group	*Total having toxemia or symptoms only*	*Cases of eclampsia or preeclampsia: Number*	*Cases of eclampsia or preeclampsia: Per cent*
Obese, overweight 20% or more	78	10	12.8
Control	24	6	25.0
Vitamin	24	3	12.5
Protein	13	0	0
Prot. + Vit.	17	1	5.9
Nonobese	267	31	11.6
Control	98	16	16.3
Vitamin	67	7	10.4
Protein	53	7	13.2
Prot. + Vit.	49	1	2.0

Overweight patients had a greater frequency of preeclampsia and stillborn children with a lessened frequency of puerperal morbidity. Toxemia was more common among those patients whose intake was especially high during the second trimester. With respect to seemingly positive correlations between complications and a low protein or low calorie consumption, it was felt that toxemia was the cause rather than the result of inadequate intake. Plasma proteins seemed, if anything, higher among patients subsequently beset by complications. Significantly, dietary intakes in excess of recommended allowances and vitamin supplementation exerted no apparent favorable influence on perinatal experience.

The Vanderbilt investigators emphasized the wide variation in both laboratory and clinical parameters of apparently uncomplicated pregnancy. In identifying particularly those determinations affected by [illegible]dilution, they espoused caution in evaluating phenomena that, although [illegible] in the non pregnant population, may be without significance [illegible]ing ge[illegible]tion.

Darby's group considered the possibility—also advanced by others—that the overall nutritional status of their patients on entering pregnancy may have been above any level required to precipitate overt disease. Actually, their results may mean only that the influence of adequate nutrition is not increased materially by additional specific nutrients. These observers believed that the only proved associations were between adverse effects and nutritional disorders of demonstrable etiology, which were readily distinguishable from disease of pregnancy of non-nutritional origin. However, they did state that, "We do not wish to be interpreted as concluding that nutrition is unimportant in pregnancy. There is no question that pregnancy can be influenced by nutritional deficiencies and that the health of the offspring can suffer from maternal malnutrition."

OTHER OBSERVATIONS

Confusion concerning the relationships of prenatal diet to weight gain, and of each of these to the complications of pregnancy is compounded by other, including more recent, reports. Crump[43] *et al.* have actually questioned the association between infant birth weight and the mother's weight at conception. Fish[44] and his associates concluded that "excessive pregnancy weight gain and toxemia should be largely dissociated." Crucial emphasis is placed on the non-specificity of "weight," in the absence of detailed information on body composition—a consideration compromising its value as a parameter of patient status (Seitchik and Alper,[4] Haley and Woodbury[45]). Reports by McCartney *et al.*[47] and by Plentl and Gray[48] indicate that toxemia is associated with an excess of exchangeable sodium in the fat-free tissue components. Smith *et al.*[49] have demonstrated altered serum protein patterns by electrophoresis. Werch[50] and associates found low serum protein values associated with poor protein intake. Macy and her coworkers[51] have provided a much needed physiological frame of reference through a mass of observations on pregnant women. Appropriately, Stearns,[52] and more recently, Soichet[53] have emphasized the effects of emotional stress on maternal metabolism and the occurrence of toxemia.

Discrepancies in these and other reports reflect the difficulty of defining, identifying and evaluating nutritional—as distinct from non-nutritional, factors. Emphasis on the relation of *prematernal* nutriture to the development of nutritional and related disorders during pregnancy, and on the need to consider this influence on perinatal events (Moriyama[54]), underscores the practical importance of satisfactory dietary practices long before marriage—from the time of the mother's own growth and development, conceivably even before. "The possibilities of cumulative effects of malnutrition in population groups over long periods of time have been subject to much comment but little serious investigation. In many cases, the great ability of organisms to recover from malnutrition of various kinds is impressive."[55]

ANEMIA IN PREGNANCY

The generic problem of standardizing diagnostic criteria and, especially of distinguishing between physiological and pathological, maximal and

optimal, usual and normal, acceptable and desirable conditions, is nowhere more apparent than in a consideration of the "anemia of pregnancy" Notwithstanding considerable common agreement on measurements and mechanisms, clinicians differ on the question of significance and, particularly, of practical management and prevention of a low hemoglobin level during gestation

Numerous observers have associated anemia in pregnancy with adverse effects, both fetal and maternal (Traylor and Torpin,[56] Giles and Shuttleworth,[57] McLean,[58] Zilliacus and Putkinen,[59] Sisson and Lund,[60] Raiha *et al* [61] Tompkins *et al* [40]) A causal relationship is implied, although a common denominator may be implicated The several anemias of pregnancy are characterized by different morphological and clinical attributes and by different, necessarily interdependent etiologies Most, if not all, *of these are obviously not unique to pregnancy, but, more probably*, precipitated by and exaggerated during, gestation They frequently coexist with consequent hematological confusion resolved only by extensive laboratory investigation and/or therapeutic trial

Although macrocytic anemias of pregnancy are common in India and have even been credited with a significant frequency in the United Kingdom (Giles and Shuttleworth,[57] Chanarin *et al* [6]), they do not as such, constitute the major problem in this part of the world Concern here is principally with the hypochromic, normocytic (usually) anemia which is so commonly encountered as to be considered, if not normal, certainly not remarkable

This problem is fundamentally one of the so called physiological anemia of pregnancy (Holly[63]) Hemodilution undoubtedly occurs in normal pregnancy, with hemoconcentration following in labor and the puerperium (Miller *et al* [64]) estimates place the transitory increase in circulating plasma at 20 to 40 per cent and that of circulating hemoglobin at about half that figure (to 17 per cent), in a majority of untreated cases However, abundant evidence (Edgar and Rice,[65] Gatenby,[66] Fisher and Biggs [68] Benstead and Theobold,[68] Kerr and Davidson,[69] Holly[63]) suggests that in most instances a fall in hemoglobin can be prevented, or at least limited by adequate supplies of iron On occasion prematernal stores appear ample as in certain Bantu mothers, who, despite, a generally unsatisfactory nutritional state characteristically maintain normal hemoglobin readings throughout gestation [70]

The routine administration of iron throughout pregnancy, even before the third trimester brings enhanced absorption, has been questioned as unnecessary and possibly contraindicated (Lapan and Friedman,[71] Hytten and Duncan[7]) but the difficulty if not the impossibility, of distinguishing between ostensibly normal and abnormal features of the maternal state moves many observers to advocate this procedure In the relatively few patients with impaired iron absorption (estimated 8%) or decreased tolerance (estimated 4 to 13% depending on the preparation), parental therapy is almost always effective (O Sullivan *et al* [73] Pritchard [74] Scott and Govan [75] McClanahan *et al* [76]) Ascorbic acid may enhance iron absorption Pyridoxine, folic acid, vitamin B_1 and other adjuncts are rarely employed in the absence of some condition unrelated to, but com-

plicated by pregnancy. In some areas, however, supplements of these modalities and of proteins are not uncommonly indicated (Spies,[77] Berry[17]).

To the extent that anemia may actually contribute to, and not merely share a common etiology with, increased perinatal and neonatal morbidity, it is conceivable that more intensive efforts towards its prevention may represent the thus far most practical device for improving these statistics. Continued laboratory and clinical investigations promise increased clarification of this and related nutritional problems in pregnancy. More basic metabolic studies continue to further understanding of the roles of such micronutrients as vitamin B_6, vitamin B_{12}, and folic acid during this period of stress.

B-VITAMIN STUDIES IN HUMAN REPRODUCTION

Sprince,[78] Wachstein,[79] Darby,[4] and others have presented evidence for increased pyridoxine needs during gestation. An excess of intermediate metabolites of tryptophan (N-methyl nicotinamide, kynurenine, *etc.*) has been noted in the urine of pregnant women, many of whom also excrete increased quantities of xanthurenic acid following ingestion of relatively large amounts (10 gm.) of dl-tryptophan. This latter phenomenon has been observed more commonly in cases of toxemia and reversed by administration of pyridoxine (10 mgm. daily). Pyridoxine load tests have shown no difference between toxemia and non-toxemia patients, although pregnant women in general exhibit a reduced output compared with non-pregnant controls. To date there is no satisfactory evidence that the routine administration of pyridoxine during pregnancy affects the occurrence of toxemia and other complications.

Evidence for a relationship between vitamin B_{12} and the outcome of human gestation is also indirect and inconclusive. Beyond correction or improvement of macrocytic anemias as reported by Chaudhuri[80] and by Patel and Kocher,[81] administration of this vitamin may prove to exert an important influence on specific aspects of the reproductive process. Chow[82] and his associates have demonstrated enhanced absorption of vitamin B_{12} during pregnancy. The plasma level of this substance is lower in pregnant than non-pregnant women, decreases throughout pregnancy, and is lower in the mother at term than in her newborn child. Doses of up to 100 micrograms daily fail to prevent the decline in maternal plasma levels; however smaller doses maintain levels comparable to the non-pregnant state when supplemented with folic acid. A rapid succession of pregnancies seems especially to deplete maternal stores of vitamin B_{12}, so that the plasma level is depressed even in the interpregnancy period. Sorbitol and calcium salts appear to enhance B_{12} absorption under certain circumstances (Chow *et al.*,[82] Boger *et al.*,[83] Herbert *et al.*[84]).

Folic acid metabolism appears altered in pregnancy, even in the absence of the megaloblastic anemia that it commonly corrects (Chanarin *et al.*,[85] Spies,[77] Scott[86]). Compared with non-pregnant controls, pregnant women show an increased rate of clearance of intravenously administered folic acid, notably in the last trimester. Plasma clearance is especially rapid in instances of twin pregnancy and of megaloblastic anemia. A deficiency

appropriate adjustments, to continue it during the intervals between ıancies

efully, she will also be motivated to encourage good dietary practices members of her family—especially the prospective mothers of her ldren

DIFT IN PREGNANCY—FOOD GUIDE

ıten daily

1 quart of whole milk, or 1 quart of skimmed milk (for weight control) Skimmed milk powder may be used as a substitute for or supplement to, liquid milk (*e g*, 1–2 tablespoons added to one glass of milk) 1 oz of cheddar cheese may be substituted for 1 glass of milk

At least 1 daily

6–8 ounces of lean meat (beef veal, lamb, chicken, turkey or fish), preferably in two servings Organ meat (liver, kidney) should be substituted twice weekly

2 tablespoons of butter margarine or vegetable oil

ıl 2 slices of whole grain or enriched bread, plus ½ cup of enriched or cooked whole grain cereal (One extra slice of bread may be substituted for cereal)

(*a*) Potato, 1 medium (¾ cup of cooked rice noodles, spaghetti or macaroni may be substituted twice weekly) (*b*) Dark green or deep yellow vegetable, average 1 cup (*c*) One other vegetable, raw or cooked, average 1 cup, except peas beans, corn, lentils, beets (½ cup)

(*a*) Citrus fruit (2 oranges or 1 grapefruit), or citrus fruit juice 8 oz Tomato juice (8 oz) may be substituted for 1 orange ½ grapefruit or 4 oz citrus fruit juice (*b*) One fresh fruit or ½ cup cooked or unsweetened fruit Prunes (4–5) or dried apricots (5–6) may be used

t One serving of simple pudding with milk, eggs and fruit (if desired)

Ienu

t Citrus fruit (2 oranges, 1 grapefruit) or 8 oz of citrus fruit juice (Half may be reserved for later in the day)
1 Egg
½ cup of cereal or 1 slice of toast
(½ pat of butter)
1 glass of milk

2–3 oz of meat fish or poultry
1 vegetable raw or cooked
1 slice of bread
½ pat of butter
1 fruit
1 glass of milk

0 8 pounds per week seems a reasonable goal However, the limitations and non-specificity of unqualified scale readings should be emphasized Notwithstanding recent, provocative support for a large *salt intake*,[56] many observers favor some limitation of dietary sodium during pregnancy Until its metabolic role is better understood, salt probably should not be restricted routinely A daily intake of 2 5 to 5 0 grams of salt (*more in summer months*) probably should be allowed in the absence of specific contraindications such as diabetes mellitus, hypertension, etc in amounts recommended by NRC 1958

Supplements —Multivitamin supplements (1 to 2 times the NRC recommendation) seem warranted to provide an extra margin of safety during pregnancy and lactation Although supplementation probably is not necessary in all, or even most, instances where a good diet is assured, it is impossible at present to satisfactorily identify patients and/or conditions presenting abnormal requirements Moreover, the crucial and irretrievable first 40 weeks of a new individual's existence permit neither deliberation nor experimentation

Iron supplements also seem indicated in all pregnant women, especially those with a history of anemia, multiple births frequent pregnancies or a low hemoglobin level, (below 12 grams per cent) Beyond the seeming advantages of a sustained, satisfactory concentration throughout pregnancy—notably in women whose metabolisms are accustomed to a usual high normal range—this practice seems warranted by the frequency and *unpredictability* of complicated delivery (*e g* , cesarean section, intra and postpartum hemorrhage) Adequate reserves of iron, together with protein and other essential nutrients, conduce to rapid recovery and to early establishment of the mother's capacity to nurse and to otherwise meet the needs of the newborn infant Oral preparations, providing 100 to 110 mgm of elemental iron daily are usually effective, especially during the third *trimester* * *Intramuscular preparations are suited to* instances of alimentary intolerance and of low hemoglobin levels close to term Ascorbic acid and pyridoxine supplements may also be indicated in some instances of refractory anemia The less common macrocytic anemias warrant more detailed evaluation before prescription of folic acid vitamin B_{12} or other, possibly specific modalities

Although calcium salts have been described as beneficial in limited instances, notably in the management of leg cramps, supplementation seems unnecessary where the daily calcium intake is 1 5 grams (2 0 grams during lactation) through usual food sources notably milk products When indicated the lactate or gluconate form seems preferable—at least until the action of phosphate preparations is better understood The possibility that large quantities of milk may interfere with *iron absorption* should always be considered Phosporus free calcium is best for leg cramps

Apart from concern for an adequate iodine intake under certain circumstances, other mineral supplementation rarely needs to be considered in uncomplicated pregnancy

The patient should be encouraged to adopt a good nutrition program at the beginning of pregnancy, to maintain it throughout lactation, and,

*Ferrous gluconate 15 gr daily or Ferrous Sulfate 9 gr daily are frequently employed

with appropriate adjustments to continue it during the intervals between pregnancies

Hopefully, she will also be motivated to encourage good dietary practices among members of her family—especially the prospective mothers of her grandchildren

DIET IN PREGNANCY—FOOD GUIDE

Foods to be eaten daily

(1) Milk	1 quart of whole milk, or 1 quart of skimmed milk (for weight control) Skimmed milk powder may be used as a substitute for or supplement to, liquid milk (*e g*, 1–2 tablespoons added to one glass of milk) 1 oz of cheddar cheese may be substituted for 1 glass of milk
(2) Eggs	At least 1 daily
(3) Meat	6–8 ounces of lean meat (beef, veal, lamb chicken, turkey or fish), preferably in two servings Organ meat (liver kidney) should be substituted twice weekly
(4) Fat	2 tablespoons of butter margarine or vegetable oil
(5) Bread and Cereal	2 slices of whole grain or enriched bread, plus ½ cup of enriched or cooked whole grain cereal (One extra slice of bread may be substituted for cereal)
(6) Vegetables	(*a*) Potato 1 medium (¾ cup of cooked rice noodles, spaghetti or macaroni may be substituted twice weekly) (*b*) Dark green or deep yellow vegetable, average 1 cup (*c*) One other vegetable, raw or cooked, average 1 cup, except peas beans, corn lentils, beets (½ cup)
(7) Fruit	(*a*) Citrus fruit (2 oranges or 1 grapefruit) or citrus fruit juice, 8 oz Tomato juice (8 oz) may be substituted for 1 orange ½ grapefruit or 4 oz citrus fruit juice (*b*) One fresh fruit or ½ cup cooked or unsweetened fruit Prunes (4–5) or dried apricots (5–6) may be used
(8) Dessert	One serving of simple pudding with milk, eggs and fruit (if desired)

Sample Menu

Breakfast	Citrus fruit (2 oranges, 1 grapefruit) or 8 oz of citrus fruit juice (Half may be reserved for later in the day) 1 Egg ½ cup of cereal or 1 slice of toast (½ pat of butter) 1 glass of milk
Lunch	2–3 oz of meat fish or poultry 1 vegetable raw or cooked 1 slice of bread ½ pat of butter 1 fruit 1 glass of milk

Dinner	4–5 oz of meat fish or poultry 1 medium potato ½ pat of butter 1 green or yellow vegetable 1 vegetable salad, if desired 1 milk dessert or fruit 1 glass of milk	Coffee and tea to 3 cups as desired, with added milk to come from total allowance
Snack (Mid afternoon or evening)	1 glass of milk 2 Graham crackers	

Extra fruit and bread to be added in accordance with caloric needs Ice cream may be permitted twice weekly, if not contraindicated Many women will do better on frequent small feedings than on 2 or 3 large ones Menu should be flexible, providing for appropriate substitution and exchanges Specific menu prescription should be governed by considerations of individual requirements, weight gain, and sodium allowance Concern for blood lipid status would necessitate modification of whole milk, egg and other animal fat products

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Chapter 35

Nutrition in Infancy and Adolescence

By L. Emmett Holt, Jr.

NUTRITION IN INFANCY

Peculiarities of Nutrition in Infancy.—The general principles of nutrition are discussed elsewhere in this book. Here we shall consider how these are modified by the phenomena of growth and maturation. Growth, it may be pointed out, involves more than an increase in size. It involves changes in function and in body composition, both of which are reflected in nutritional requirements.

In relation to his size the infant needs more of all nutrients. He requires nutrients for growth and in addition, because of his higher metabolic rate and more rapid turnover of nutrients, his requirements for maintenance are higher than that of the adult. His relatively large surface area involves relatively greater losses of heat and water through the skin. The development of the skeleton imposes special nutritive requirements. The absence of teeth requires that his food be finely subdivided. In contrast to these handicaps there are certain nutrients in regard to which he is in a favored position, having received during fetal life a surplus which is stored in the liver and which will tide him over the early months. Iron, copper and vitamin A are in this category.

Nutritional Requirements in Early Life.—*Energy Requirements.*—The caloric requirements of the newborn infant are 2 to 3 times as great as those of the adult in terms of body weight. Average figures for boys are given in Figure 72, which also indicates the distribution of calories needed during the period of growth. The basal heat production of the infant is high; this is due in part to his relatively greater body surface which favors loss of heat by conduction and convection, in part to his larger proportion of active metabolic tissue. It should be pointed out that what is commonly referred to as basal metabolism—namely metabolism under conditions of rest—is actually not basal in the growing child, for it represents the energy required for growth as well as for maintenance. Energy required for growth is greatest in the newborn period, decreasing rapidly during the first year and more gradually up to the time of puberty, when a spurt in growth occurs. The requirement for activity is suprisingly great even in small infants; crying alone has been shown to double the metabolic rate.[1] The energy lost in the excreta is somewhat greater in early infancy than later; this, however, represents only a small fraction of the total energy requirement. There is considerable variation in the caloric requirements of individual infants, due chiefly to differences in activity. A placid infant may thrive on as little as 70 calories per kg., whereas one who cries a great deal may require 130 calories or even more.

Protein Requirements —Protein is required for maintenance (wear and tear) of tissues for growth of new tissue and for maturation of tissues At birth roughly 2 per cent of the body consists of nitrogen as contrasted with 3 per cent for the adult Most of this change occurs during the first year Tentative minimal requirements for high quality *protein at different* ages are shown in the accompanying figure (Fig 73) It would appear that breast milk, which commonly furnishes an intake ranging between 2 0 and 2 5 grams per *kilo*, provides only a small margin of safety, however, its quality, constancy of composition and regularity of administration render this small margin adequate Cow s milk was formerly regarded as considerably inferior to breast milk in biological value and for this reason

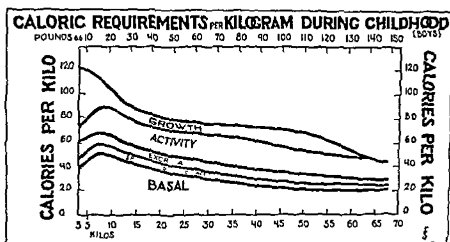


FIG 72 —Caloric requirements per kilogram throughout childhood The ordinate under the upper curve shows the average requirement in calories per kilogram The space between the various curves indicates the allowance for the various factors which make up the total (Holt *Pediatrics* courtesy Appleton Century Crofts)

higher protein intakes have been commonly given Recent work, however, has shown that *when cow s milk is processed in such a way as to avoid curd indigestion* the protein is utilized virtually as efficiently as that of breast milk, and that intakes greater than 2 5 grams per kilo are not necessary

Beyond the period of infancy the curve of protein requirement falls off sharply more sharply than the curve for caloric requirement The reason for this is that activity is now the major function for which calories are required and activity unlike growth and maintenance, does not involve additional expenditure of nitrogen The widely used formula that 15 per cent of the total calories should consist of protein a proportion which obtains in most American diets at all ages appears to provide protein well in excess of minimal requirements in infancy and even more so as the child grows older It should be borne in mind however that on a mixed diet in which much of the protein is of vegetable origin one which varies from meal to meal and which presents mastication problems a greater margin of safety is needed than is the case with a milk diet An excess intake of 50 per cent above the minimum requirement has been recommended for aver-

age mixed American and European diets[2] When the dietary protein is derived almost exclusively from a single vegetable source, as is the case in certain underdeveloped countries, it may be difficult to provide enough to meet the protein requirements because of the large quantity required, and manifestations of protein deficiency are commonly encountered

Amino Acid Requirements —The requirements of infants for essential amino acids as determined by Snyderman *et al*[3] on a synthetic diet prepared with pure L-amino acids are given in Table 144 From this it appears

TABLE 144 —ESSENTIAL AMINO ACID REQUIREMENTS OF INFANTS

Amino acid	*Minimal requirement of the young infant** (*mg /kg /day*)	*Intake of typical 3 mos old breast fed infant* (*mg /kg /day*)
L-histidine	23	31
L-isoleucine	120	132
L-leucine	154	254
L-lysine	105	124
L-methionine	34†	33
L-phenylalanine	90	115
L-threonine	60	106
L-tryptophan	22	36
L-valine	105	144

*As determined by Snyderman *et al*[3]
†Based on a single observation only

that breast milk in quantities commonly ingested provides a moderate but not a large margin of safety for each essential amino acid so studied The requirements for essential amino acids, like those for protein, are relatively high in early life this is due in part to the demands for growth and in part to higher maintenance requirements

Amino Acid Balance[4]—The requirements for specific amino acids are not constant under all conditions *On low protein intakes* the proportions between individual amino acids becomes important Under these circumstances *an optimal amino acid pattern is needed for the most economical* use of the amino acids Several excellent amino acid patterns have been suggested as standards of reference, but as yet none has been shown to be superior to the amino acid pattern of milk

Fat Requirement —There is some evidence that humans like other animals require small quantities of polyunsaturated fatty acids The long continued use of a fat-free diet has been followed by undesirable consequences Chwalibogowski[5] fed 2 infants on a fat-free diet for more than a year Their clinical course and development did not appear in any way abnormal although some evidence of rickets was obtained Hansen and Wiese[6] maintained a child with chylothorax on a fat-free diet for two years and observed increased frequency of skin infections and the development of eczema More recently they studied a group of premature infants[7] maintained on a fat-free diet in whom a scaly dermatitis developed The addition of small amounts of poly unsaturated acids to the diet cured this condition

The older pediatric literature contains many references to the deleter-ious action of volatile (short chain) fatty acids, and their higher concen-ation in cow's milk has been blamed for some of the shortcomings of rtificial feeding, but the evidence does not bear critical analysis It now ppears that the short chain fats are digested as well as, if not better than, ieir long chain analogs Short chain fats and fats containing unsaturated nkages are somewhat more readily absorbed [8 9] In feeding normal infants appears desirable to include a certain amount of fat in the diet, but a rong case for feeding particular fats cannot be made, for the differences re very small In conditions of steatorrhea, however, the superior ab-orption of cert in fats appears to have some practical advantage

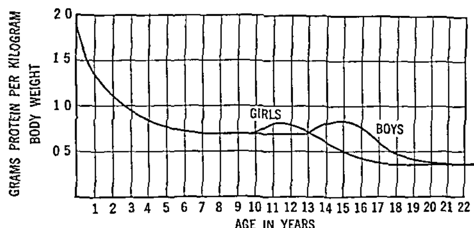


FIG 73 —Protein Requirement of Reference Protein at Different Ages
F A O 1957 [2]

Carbohydrate Requirement —Although infants have been fed on carbo ydrate-free diets for many months,[5] this is never attempted in practice he development of ketosis is difficult to avoid As a rule roughly half of n infant's caloric requirement is supplied as carbohydrate

Mineral Requirements —These are, for the most part, not accurately efined With the exception of iron the breast fed infant appears to be dequately provided with minerals and it may be assumed that the quanti es ingested are well above his minimal requirements A 12-pound infant igesting 800 cc breast milk per day would receive the following quantities f minerals

	Intake				*Per cent of intake retained*
	mg /day	*mg /kg /day*	*mM /day*	*mM /kg /day*	
a	120	21 6	5 2	0 95	40–55
	420	75 7	10 8	1 96	20–30
a	250	45 0	6 2	1 13	15–20
Ig	30	5 4	1 2	0 22	20–30
l	330	59 2	8 4	1 53	20–30
	200	36 0	6 4	1 16	15–20

)eficits of these minerals do not ordinarily arise from inadequate intake, hey may, however, arise from pathologic processes in which there are

abnormal losses of electrolytes from the gastrointestinal tract, kidney and, at times, the skin

The only important mineral deficiency likely to be encountered in feeding normal infants is that of iron, which is seen in infants fed exclusively on milk for more than the first few months Both cow's milk and breast milk provide insufficient iron and when the stores present at birth become depleted, iron deficiency anemia develops unless a supplement is given It is the current practice to give such a supplement either as natural solid food, as a reinforced cereal, or in the form of medicinal iron, beginning in the second or third month of life Before this time dietary iron is not readily utilized The supplement should provide a total iron intake of 4 to 6 mg per day and should be continued until a mixed diet is well established

Under exceptional circumstances when a milk-free diet must be used for fortification of the diet with calcium may be advisable An intake of 200 to 300 mg per day appears to be adequate

A factor complicating the exact determination of mineral requirements is the phenomenon of 'supermineralization ' When more mineral is given more is retained and the body may become for a time at least, richer in mineral This phenomenon is particularly striking in the case of calcium and phosphorus and it appears that hyperalimentation of these elements may temporarily increase their storage in the bones Whether this is beneficial or not is not established Some observations made in animals[10 11] suggest that calcium more rapidly acquired during the growth period is more loosely held in adult life and may predispose to senile osteoporosis Evidence that this holds for man is not available

Among the trace elements fluorine has recently assumed considerable importance An excess of this element leads to discoloration and mottling with increased brittleness of the dental enamel (fluorosis) whereas a deficiency predisposes to dental caries The margin of safety between the two is a relatively small one It has been estimated that if drinking water contains less than 1 ppm* of fluorine cariogenic effects may be expected A concentration between 1 0 and 1 5 ppm is thought to be ideal[1] Concentrations up to 2 ppm may lead to white mottling beyond this level brown mottling and fragility of the teeth may be encountered Milk itself may contain as much as 2 ppm of fluorine but this does not lead to fluorosis since the fluorine exists in an insoluble form The control of the fluorine content of drinking water has become a public health problem (see Chapter 20) it is a matter of particular importance during the period of dental development

Vitamin Requirements —The requirements of infants for the vitamins which are established as dietary essentials are given in the following table

Vitamin A	Not accurately known 1500 i u per day is definitely protective
Vitamin C	25 mg per day[13]
Vitamin D	400 i u per day[14]
Thiamine	0 20 mg per day[15]
Riboflavin	0 50 mg per day[16]
Pyridoxine	0 50 mg per day[17]

* Part per million

The requirement for nicotinic acid is a conditional one. If the intake of tryptophan is sufficient it appears that the nicotinic acid required can be synthesized from this source. However, when the protein intake is marginal, nicotinic acid must be supplied as such. The requirement is commonly expressed in terms of niacin equivalents, 60 mg. of tryptophan being equivalent to 1 mg. niacin. Another B factor for which the requirement is conditional is choline. With a sufficient intake of methionine the needs of the body for additional choline appear to be insignificant, but, when the intake of methionine is limited, choline becomes a dietary factor of importance. The quantitative relationships between these conditionally required factors and their antecedents remain to be accurately defined.

It is possible that extremely small amounts of folic acid and B_{12} are needed by the human organism. These vitamins are synthesized in the large intestine, but it is questionable if they can be absorbed from the large gut in significant amounts. B_{12} requires no consideration in the infant's diet, nor does folic acid provided the diet contains an adequate amount of vitamin C and provided antibiotics are not being given.

Other known B factors—pantothenic acid, biotin, and inositol—important as they are catalysts in metabolic reactions, are not yet established as normal dietary essentials. The same is true of lipoic acid (thioctic acid).

In infant feeding, ascorbic acid and vitamin D are the chief factors which merit concern. In sterilizing milk much of the ascorbic acid is destroyed, hence it is regarded as good practice to provide the daily requirement by means of a vitamin supplement or by orange or tomato juice. A number of proprietary feedings are now fortified with adequate amounts of C.

Since unfortified cow's milk and even breast milk can not be relied on to furnish adequate vitamin D, this must be supplied independently or some fortified milk used.

Vitamin A deficiency is seen in infants only under exceptional circumstances, as when skimmed milk has been employed for feeding for a prolonged period. A few years ago pyridoxine deficiency was observed in infants fed a proprietary feeding which had been subjected to unusual thermal treatment.[18,19] This defect was soon corrected and with the recognition of this possible deficiency it appears unlikely that it will recur.

Water Requirement.—The infant is peculiarly susceptible to lack of water. His obligatory water loss through the kidney and the skin is considerably greater than that of the adult and in addition he is far more subject to pathological processes causing water loss, notably vomiting and diarrhea. Symptoms of dehydration appear rapidly and have serious consequences. For the healthy infant, in a temperate climate, the minimum water requirement is probably in the neighborhood of 75 cc. per kg. A daily intake of 150 cc. per kg. (2¼ ounces per pound) may be regarded as providing an adequate margin of safety, but under subtropical or tropical conditions this may have to be increased to 175 cc. per kilo or even more.

Breast Feeding.—Many good and some poor arguments are adduced in support of breast feeding and the subject is surrounded with a certain amount of emotionalism. For most mothers successful nursing is a satisfying emotional experience and is to be encouraged from that point of view

unless there are reasons to the contrary From the point of view of the welfare of the child the writer is not impressed with the views of certain psychiatrists that failure to nurse at the mother s breast will cause emotional deprivation and subsequent psychologic maladjustment The advantage to the child is in the somatic field The strongest argument for maternal nursing is that it is a relatively foolproof method When artificial feeding is carried out under ideal conditions—by an intelligent and careful mother or nurse, under experienced medical guidance and with a milk supply that is beyond question—the risk is a negligible one, but under less ideal conditions the infant may suffer and the morbidity and mortality of the artificially fed infant may run far ahead of the breast fed It is obvious that in some countries, in some areas and with some groups of people the encouragement of nursing is a matter of the greatest importance

Breast Feeding vs Breast Milk —How much of the over-all superior results with breast feeding are due to the safety of the method and how much to the superior nutritional qualities of breast milk is a much debated question Adequate data on infants artificially fed on human milk obtained from a breast milk dairy would settle the matter but such data are not available In their absence, conclusions must be drawn from data where artificial feeding is carried out under ideal circumstances and from biochemical and nutritional studies of the two milks As stated above, the results of ideal artificial feeding appear to be comparable to those of breast feeding One can state with assurance that the important nutritional differences have been overcome It is possible however, that factors of minor importance remain to be discovered in which breast milk may possess some small advantage One or two claims for such substances [0,21] have recently been made, but await confirmation

Practical Considerations in Breast Feeding —Nursing should not be attempted if the mother herself is not in good health The additional strain may further injure her health and her milk production is likely to be inadequate With a recent history of tuberculosis it is unwise to attempt nursing other contraindications are severe complications of labor and infection of the breast

A satisfactory routine to establish the milk supply is to allow the mother a twelve-hour rest after parturition after which the baby is put to the breast at four hour intervals being allowed several minutes at each breast The milk usually comes in in abundance on the third day although it may be delayed beyond this Not infrequently the milk comes in with a rush and the supply may exceed the demand, leading to engorgement of the breasts However the supply soon adapts itself to the needs of the child

Regularity of nursing hours helps to establish and maintain lactation Although some psychologists and pediatricians have stressed 'self demand" feeding—allowing the child to nurse whenever and as long as he pleases, lest he be frustrated it is the opinion of the author that this doctrine has been overstressed Infants can readily be trained to a schedule of feeding in fact left to themselves the majority will do so A regular nursing time is a convenience to the mother Once the milk supply is well established it has been shown that only a few minutes (often less than five) are required for the baby to empty it prolonged nursing increases the chance of damage

to the nipples and infection of the breast When the milk supply is well established it is not necessary to use both breasts at a feeding, their alternate use spares the nipples However, when the milk supply is inadequate, both breasts should be used, the more frequent stimulation of the nipples serves to increase the flow of milk

Successful nursing is indicated by a normal gain in weight and freedom from digestive disturbances If the infant fails to thrive, an inadequate milk supply should be suspected, the amount of milk obtained by the baby is determined by weighing him before and after nursing If the quantity of milk is sufficient, it may be assumed that its quality, too, is satisfactory, very exceptionally drugs or other noxious substances taken by the mother will make the baby ill

If it is found that the baby is obtaining insufficient milk to meet his caloric requirements * steps should be taken to increase the maternal milk supply and temporarily at least, to supplement it with a bottle feeding Hormone therapy offers little in the way of increasing the milk supply The mother must, of course, have an adequate diet Two factors of the greatest importance are freedom from emotional stress and proper emptying of the breast Under the influence of emotion the phenomenon of "let down" of milk is interfered with,[2] the milk does not pass from the acini to the collecting ducts from which it can be expressed, and lactation is suppressed Every effort must therefore be made to eliminate psychologic factors that may be upsetting the mother Maximum emptying of the breast may be obtained by having the baby nurse on both breasts at each feeding, following this by a bottle In some instances the baby experiences difficulty in emptying the breast because of retracted nipples or because of some anomaly of the collecting duct system In such instances a breast pump or mechanical expression of the milk may be more effective in emptying the breast and maintaining its secretion, the deformity can often be corrected to some extent by such mechanical means As a rule, if after a reasonable attempt no more than half the caloric needs can be met by the maternal supply, it is best to wean the infant

A common cause of unnecessary weaning during the early weeks of lactation is the belief that the milk has suddenly lost its nutritive quality Mothers will often state that during the second or third week their milk "suddenly turned to water" and that on this account the baby was weaned often with the doctor's advice It is not generally understood that the change in the appearance of the milk, particularly of the first drops of mature milk which may appear spontaneously at the nipples, is a normal one The early secretion—colostrum—though small in amount is rich and creamy in appearance, being high in protein and fat, whereas mature milk is considerably thinner Moreover, the first drops of mature milk are very low in fat the appearance being slightly bluish, resembling skimmed milk As the nursing proceeds the fat concentration rises and the terminal part of the feeding which the mother does not ordinarily see may be creamy with

* Breast milk may be assumed to provide 20 calories per oz and the caloric requirements of the child may be assumed to be between 70 and 130 calories per kg, depending upon his activity (see above)

a high fat content Unnecessary concern and often unnecessary weaning can often be avoided by acquainting mothers with this phenomenon

Vitamin supplements are commonly given to breast fed infants—orange juice (1 oz a day) or 25 mg of ascorbic acid being given to meet the requirement for vitamin C and 400 units of vitamin D being given as cod liver oil or some concentrate It must be admitted, however, that even without such supplements scurvy is almost unknown in the breast fed infant, and rickets, except in the Negro, is rare Solid foods are now commonly started in the third or fourth month—in part for their educational value and in part because they provide iron These are further discussed in connection with artificial feeding

Few American babies are nursed beyond the age of four months, although there is no objection to continuing nursing to the age of eight or nine months provided solid foods are given as supplements Unless there is some indication for sudden weaning such as acute illness on the part of the mother, weaning should be done gradually One nursing at a time should be dropped out and replaced by a bottle feeding, after a pause of several days another may be similarly replaced the weaning being completed in the course of two or three weeks Such gradual weaning prevents the discomfort from breast engorgement which occurs with sudden weaning

The diet of the nursing mother must be sufficient to cover her own needs and those of the child as well Exact figures for food requirements cannot be given and in their absence recommended allowances are usually generous In the great majority of instances the mother s appetite increases with her caloric needs at this time subsiding again at the time of weaning There is rarely any need of control on the part of the physician It is not necessary that the mother drink as much milk as she is furnishing On a milk free diet mothers may go into negative calcium balance hence some milk is desirable, unless some other means of maintaining the calcium intake is undertaken It appears however that a milk intake equivalent to one-half of her own output is altogether adequate to supply the calcium need The mother s diet should be balanced and adequate in protein and calories but if these conditions are met there appears to be no need for special vitamin supplements It is important to provide the additional calories lost in the milk

Artificial Feeding —Successful artificial feeding with cow s milk involves three problems (1) meeting the nutritional requirements of the child, (2) avoiding certain mechanical difficulties of digestion caused by the curd of the milk and (3) avoiding pathogenic microorganisms The bacteriologic problem is solved by heat treatment of the milk—pasteurization boiling or autoclaving and by scrupulous care of the utensils, nipples and bottles all of which are heat sterilized Cleanliness on the part of the mother or nurse in preparing and giving the feeding is also essential

The curd problem too is conveniently solved by heating the milk This causes the lactalbumin to coagulate in fine particles, the subsequent coagulation of the casein in the infant's stomach occurs about these micelle and the resulting curd is friable and easily digestible rather than tough and resistant The beneficial effect varies with the amount of heat applied Pasteurization improves the digestibility of the curd, but does

not overcome the difficulty completely, as does boiling or autoclaving How ever, terminal sterilization by raising the milk to the boiling temperature in the feeding bottles is now common practice, so that even when fresh pasteurized milk is used the subsequent heat treatment takes care of the curd problem The all important consideration is the nutritive property of the feeding a consideration of which demands some knowledge of the differences between cow s milk and breast milk

Differences between Breast Milk and Cow s Milk —As is shown in Table 145 cow s milk is richer in protein by reason of its higher content of casein it is comparable in fat content but contains considerably less sugar (lactose) Its mineral content is higher, individual minerals

TABLE 145 —AVERAGE PERCENTAGE COMPOSITION OF MATURE BREAST MILK AND COW S MILK*

Constituents	*Breast milk* *Per cent*	*Cow s milk* *Per cent*
Water	87 6	87 2
Total solids	12 4	12 8
Protein	1 1	3 3
Casein	0 4	2 7
Lactalbumin	0 4	0 4
Lactoglobulin	0 2	0 2
Fat	3 8	3 8
Lactose	7 0	4 8
Ash	0 21	0 71
Sodium	015	058
Potassium	055	138
Calcium	034	126
Magnesium	004	013
Iron	00021	00015
Chlorine	043	100
Phosphorus	016	099
Sulfur	014	030
Vitamin content per 100 cc		
Vitamin A	53 00 μg	34 00 μg
Carotinoids	27 00 μg	38 00 μg
Thiamine	16 00 μg	42 00 μg
Riboflavin	43 00 μg	157 00 μg
Nicotinic acid	172 00 μg	85 00 μg
Pyridoxine	11 00 μg	48 00 μg
Pantothenic acid	196 00 μg	350 00 μg
Folic acid	0 18 μg	0 23 μg
Choline	9 00 mg	13 00 mg
Inositol	39 00 mg	13 00 mg
Biotin	0 40 μg	3 50 μg
B_{12}	0 18 μg	0 56 μg
Vitamin C	4 30 mg	1 80 mg
Vitamin D	0 4 10 0 i u †	0 3–4 0 i u †
Vitamin K	26 D G units**	100 D G units**
Calories per ounce	22	21
Calories per 100 cc	71	69

* Taken largely from National Research Council Bulletin No 254 1953
** Dam Glavind units
† International units

being from 3 to 5 times as abundant as in breast milk. Most vitamins, too, are present in higher concentrations in cow's milk, exceptions being vitamins C and D, nicotinic acid and inositol.

Provided the bacteriologic problem and the mechanical problem of the curd are taken care of by the heat treatment, undiluted and unmodified cow's milk can be and is often used for infant feeding and with success. Such difficulties as are attributed to it are of a minor nature. It may require a few days for the infant to adapt to the higher protein intake if a change to whole cow's milk is suddenly made. It has also been pointed out[23, 24] that because of the higher protein and mineral content of cow's milk, infants so fed have a greater obligatory water requirement for renal excretion, hence with the same fluid intake they have a slightly smaller margin of safety against dehydration. For these reasons and also because of tradition based on experience before the curd problem was solved, the general practice has continued of diluting cow's milk to reduce its protein content, the caloric deficit being made up with a carbohydrate supplement.

In the United States evaporated milk has largely replaced fresh milk for infant feeding. It is estimated that about 80 per cent of American babies are fed on evaporated milk or on some prepared milk feeding marketed in evaporated form. The constancy of the product, its sterility and the complete avoidance of curd indigestion have because of the thermal treatment it has been given been responsible for its increasing popularity.

Modified Milks.—Commonly used and convenient modifications of this type are the following:

Evaporated milk	3 oz	Whole milk (or reconstituted whole milk prepared from milk powder)	7 oz
Water	7 oz	Water	3 oz
Cane sugar	½ oz	Cane sugar (1 tbsp.)	½ oz
	10 oz		10 oz

These formulas are approximately isocaloric with breast milk, furnishing 20 calories to the ounce. The percentage distribution of calories in breast milk, cow's milk and in a widely employed modification given above is as follows:

	P	F	C
Breast milk	8%	50%	42%
Cow's milk	20%	51%	29%
Common milk modification	15%	35%	50%

The range in percentage distribution of calories which can be used successfully in infant feeding is a wide one, there being no need to simulate closely the composition of breast milk, as was once thought necessary. By tradition more protein is commonly given to artificially fed infants but, as pointed out above, the difference in biological value between the proteins of breast milk and cow's milk, is a negligible one.[7a] Experience with feedings providing only 10 per cent of the calories as protein has been altogether satisfactory.

Carbohydrates commonly used as supplements in artificial feeding are cane sugar, lactose and maltose-dextrin mixtures. There would seem to be

little choice between them. Starch and cereals may also be used, althoug[h] their absorption is slightly less complete.

The heat treatment used in destroying bacteria in milk and in rendering the curd more digestible also exerts some untoward effects on the nutritive properties of the milk which may have to be repaired. Most important is the loss of vitamin C, much of this is lost during pasteurization and a further loss occurs during terminal sterilization, hence all artificially fed infants should be given a supplement of 25 mg ascorbic acid in some form. Boiling milk destroys some thiamine, and autoclaving even more; this vitamin is, however, amply supplied in cow's milk and, unless autoclaving has been unduly prolonged (a half hour or more), the loss is not serious. Autoclaving milk also causes some destruction of pyridoxal, the chief form of vitamin B_6 present in milk. As ordinarily carried out in the processing of evaporated milk, the loss is not serious. At high temperatures several of the amino acids, notably lysine, may react with the lactose of the milk, forming compounds which render the amino acid unutilizable by the body, although still present by analysis. This so-called Maillard or "browning" reaction again assumes significant proportions only when liquid milk has been subjected to autoclaving for half an hour or more. The possibility of thermal inactivation of a fraction of the protein is, however, a reason for using a protein intake slightly higher than that of breast milk. In the preparation of evaporated milk it has been estimated that about 11 per cent of the lysine has been inactivated.[5] Lysine is, however, present in cow's milk protein in a somewhat higher concentration than in breast milk protein and does not appear to be a limiting amino acid.[6]

A number of proprietary infant foods are available—some in powdered and some in evaporated liquid form. Some of these are simple modifications of milk with added carbohydrate, others are "humanized milks" which imitate to a greater or lesser extent the caloric proportions, the mineral content or the fat of breast milk. They save trouble in preparing the formula and several of them are adequately reinforced with vitamins. These foods are all satisfactory and convenient, the advantage of the humanized products is, however, questionable.

Practical Infant Feeding.—Feedings for an entire day are usually prepared at one time, being put into the feeding bottles, which are then terminally sterilized by standing in boiling water for ten minutes and are then refrigerated until used. Before feeding the infant the bottle is warmed to the body temperature.

The technique of feeding is important. The rubber nipple (which must be sterilized before use) must have an opening wide enough to permit the milk to drop out of the bottle without shaking. Smaller nipples cause the baby to suck in much air and may lead to vomiting. It is also important to hold the bottle at such an angle that the nipple is always full of milk and to hold the baby vertical for a few moments after feeding to enable him to "burp" and bring up swallowed air. Regularity of feeding, though it need not be made a fetish, on the whole is to be preferred, as it is with breast feeding. Some latitude may, however, be given the child as to the quantity he takes at each feeding. As a rule his appetite is an excellent guide to follow.

In planning artificial feeding for a baby one should (1) estimate the caloric requirements from the weight (roughly 100 calories per kilogram), (2) estimate the daily quantity of formula needed—from a knowledge of the calories furnished by the formula, (3) divide this into the number of feedings desired.

Most babies will require 6 feedings a day which may be given at four-hour intervals around the clock. At the age of two months a night feeding can usually be omitted and only 5 feedings given. It is wise to check the calculation of the formula to make sure that an adequate protein allowance (2.5 to 3 gm. per kg.) and water allowance (150 cc. per kg.) are provided.

An initial artificial feeding is always in the nature of an experiment. An individual baby may need more or less than the calculated requirement. A steady weight gain and the appearance of health are the best indications of success. *Provided air swallowing and consequent distention of the stomach are avoided* one can usually rely on the baby's appetite as to the quantity of food needed. If he steadily refuses some of his bottle he probably needs less and if he drinks it ravenously and cries before mealtime he probably needs more. Abnormalities of digestion are beyond the scope of this chapter.

The artificially fed infant should be given a supplement containing 25 mg. ascorbic acid, and vitamin D in some form to insure an intake of 400 international units a day. A need for other vitamin supplements on an ordinary milk formula has not been established. Individual practice varies greatly as to the time solid foods are introduced. Cereals and homogenized baby foods can be fed by spoon at any age replacing a portion of the formula feeding but there is no particular advantage in giving them to small infants. Their purpose is twofold—to provide iron and to educate the child to accept solid foods. Since the iron stored at birth takes care of the needs of the first two months, a time during which administered iron fails to induce hematopoiesis, a good case cannot be made for giving iron before the age of three months. Training to eat is likewise readily accomplished at the age of four or five months though it should not be delayed beyond the first half year. A great variety of canned meats, vegetables, fruits and soups is now available for infants. As these are introduced, calculation of calories becomes highly inaccurate and feeding by appetite becomes the rule. By the age of seven or eight months it should be possible to reduce meals to 4 a day, the last one being milk alone, and by the age of a year, 3 meals a day should suffice. As teeth come in the need for homogenized foods disappears. A typical diet during the second year is the following:

Breakfast	Fruit juice or chopped fruit
	Cereal with milk
	Egg
	Toast
	Milk
Dinner	Ground meat or fowl or boneless fish
	Potato
	Chopped green vegetable
	Dessert: pudding or fruit
	Milk
Mid-afternoon snack	A drink of milk or cracker provided this does not impair appetite at meal times

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	Toast
	Milk
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	Potato
	Chopped green vegetable
	Dessert pudding or fruit
	Milk
Mid-afternoon snack	A drink of milk or cracker provided this does not impair appetite at meal times

Supper Soup
Egg dish or spaghetti with cheese
Chopped vegetable
Chopped fruit
Buttered toast or bread
Milk or cocoa

Digestive Disturbances —A discussion of the causes, pathologic physiology and therapy of acute and chronic digestive disturbances is beyond the scope of this chapter These disturbances provide some of the most difficult problems with which the physician has to deal In the presence of vomiting, oral alimentation is out of the question and, in the case of diarrhea, its value is limited by the hyperperistalsis Parenteral nutrition must be relied on to replete stores of water and electrolyte, to correct abnormalities of acid-base equilibrium and to supply needed calories

In conditions of acute dehydration and shock, restoration of the circulation is the matter of first concern An electrolyte solution, preferably with an excess of fixed base, should be given without delay, followed by a transfusion of whole blood or plasma to maintain plasma volume The repair of extracellular fluid deficits requires the further administration of an electrolyte solution to which potassium may be added, when it is clear that the kidneys are functioning, Darrow's solution [6] is satisfactory for that purpose The quantity of fluid given parenterally must be determined empirically One can only guess at the severity of the dehydration from clinical appearances and continue intensive treatment until the signs of dehydration—particularly lack of skin turgor—have disappeared There are however, limits to the rate at which intravenous fluid can be safely administered A 5 kg infant should rarely be given more than 1500 cc by vein a day, given by continuous drip or by intermittent push infusions This corresponds to a rate of about 1 cc per minute for a continuous drip A more rapid rate, not exceeding 15 to 20 cc per minute may be employed with push infusions in which a fraction—not exceeding 250 cc —may be given at one time

Parenteral Nutrition —This becomes important whenever the requirements of the body cannot be met by the oral route To the extent that the organism cannot be nourished parenterally it must live on its own tissues At the present time, parenteral nutrition has definite limitations and it is the general experience particularly with infants, that the fatalities which occur in severe digestive disorders when these cannot be readily brought under control are due to nutritional failure The provision of water and electrolyte, of calories and of nitrogen by the parenteral route—all present problems A reasonable approximation to extracellular fluid can be given without difficulty, but the repair of intracellular deficits is far more difficult The chief minerals of intracellular fluid potassium, magnesium and phosphorus must be given cautiously for only a limited rise in their concentrations in the plasma can be tolerated Considerable experience has been obtained in recent years in the parenteral administration of potassium, largely as a result of the pioneer work of Darrow Much can be done to restore the diminished cell concentrations of this element which occur in conditions of dehydration and in other pathologic states by

giving infusions with several times the concentration of potassium found in extracellular fluid Provided the kidneys are functioning as much as 35 mEq per L may safely be given Potassium so given may at times serve to replete the cellular deficit of potassium and may favor the extrusion of abnormal amounts of sodium from the cells Unfortunately, the restoration of the K/Na balance in the cells is not a simple matter Active metabolic processes are concerned in maintaining the differences in concentration inside and outside the cell when these are deranged the cell may not be able to accept potassium[27] which is presented to it in the extracellular environment Nevertheless the provision of this element as is done in Darrow s solution [6] permits the cell to accept it when it can Relatively little effort has been made to restore intracellular magnesium and phosphorus deficits, although Butler [8] has recommended a fluid containing them for use in diabetic coma

The provision of calories in parenteral nutrition has in the past largely been confined to glucose and amino acids although fat has recently come into use In states of dehydration once the initial state of shock has been overcome, glucose is ordinarily given with the electrolyte solution in order to supply some calories The proportion of electrolyte to glucose may be varied according to the type of dehydration present, if chemical measurements of sodium and chloride are available In hypotonic dehydration at least two thirds of the fluid should be electrolyte solution whereas if the dehydration is of the hypertonic type with elevated concentrations of sodium and chloride, the proportion of electrolyte may be reduced to one third and more glucose given Spilling of glucose in the urine does not occur if its concentration in the final infusion mixture does not exceed 5 per cent When it is increased to 10 per cent or more, the loss becomes appreciable and leads to increased water excretion by the kidney which may aggravate dehydration

Levulose has recently attained some popularity as a substitute for glucose in parenteral feeding It is removed from the blood somewhat more rapidly than glucose and does not spill out so readily in the urine It appears that it can be more readily converted to glycogen However the practical advantage over glucose is minimal

Sugar alone can at best supply only about half of the caloric requirements for parenteral nutrition Some additional calories can be furnished by amino acids but an adequate caloric intake can scarcely be accomplished without the use of parenteral fat

Amino acids for intravenous or other parenteral use are available commercially in the form of protein hydrolysates Although nitrogen balance in adults and satisfactory nitrogen retention in children can be accomplished by these preparations a slightly higher nitrogen intake is necessary, presumably because the proportions of amino acids supplied are not quite ideal The sterility of the infused material must be carefully watched since amino acids provide an excellent culture medium for bacteria The need of supplying nitrogen parenterally in acute disorders has been questioned on two grounds (1) that a brief period of protein starvation is well tolerated and (2) that in the face of a caloric deficit, such as usually obtains in parenteral feeding calories have the first priority and the amino

acids are presumably deaminated and used for energy purposes rather than for growth. Cox and his co-workers[29] have, however, shown in animals that this latter contention is not valid; at all levels of inanition the administration of nitrogen favored nitrogen retention or decreased nitrogen loss. Some confirmation of these findings in infants has been reported by Calcagno *et al.*[4] The policy of ignoring nitrogen loss, though it may cause no difficulty in disturbances of brief duration, is open to the objection that the duration of the disorder usually cannot be predicted, and, in the case of the disturbance which becomes chronic, a valuable opportunity to protect the tissues from loss may have been lost.

It should be pointed out that the administration of plasma or whole blood, valuable though it may be in maintaining plasma volume, is of negligible importance from the point of view of providing nitrogen for nutritional purposes. The proteins so administered have slow turnover rates and it is only as they are degraded that the constituent amino acids become available. Amino acids given as such can, however, be rapidly used.

Fat emulsions for intravenous use, first introduced by Japanese workers[30] have recently been made available in this country. Their keeping qualities are limited and they are not altogether devoid of reactions. They are, however, valuable as a source of calories. It has been shown by isotope studies that they are rapidly burned, labelled carbon dioxide appearing in the expired air within half an hour.

Even if it were possible to provide a complete nutriment by vein, and there is evidence that this can be accomplished in the normal subject, it does not follow that the nutrition of the sick patient can be sustained. He may suffer from metabolic disturbances which interfere with the utilization of the food given parenterally; this applies not only to caloric foods but to his mineral requirements as well. Parenteral nutrition, even with its present imperfections, has however proved to be a great advance and often a lifesaving measure in diseases of the digestive tract.

Oral Feeding in Digestive Disturbances.—Vomiting presents an obvious barrier to oral alimentation, but the situation in the case of intestinal disturbances—acute and chronic diarrheas—is not so obvious and has provoked differences of opinion in regard to their management. Restriction of the oral intake has been the policy generally favored. In its support was the observation that it resulted in decreased stooling and stool losses, also the general philosophy that rest favored recovery of a disordered function. The classical experiments of Pavlov demonstrating that food stimulated gastric secretions were cited to support the danger of food administration, for with increased peristalsis it was presumed that the minerals so secreted would be largely lost and that feeding would thus lead to electrolyte deficit. The view that infantile diarrhea represented a food intoxication was widely held by French and German pediatricians during the last century and the early part of the present one and has greatly influenced American thinking.

The philosophy of rest, however, has not gone unchallenged. Coleman[33] and Dubois[34] some years ago questioned the value of resting the intestine affected by typhoid fever and their results have revolutionized the dietary treatment of that disease. Likewise in the pediatrics field

Schick and Wagner[35] in studying chronic intestinal indigestion (celiac disease) concluded that the therapy of use was preferable to that of rest of the disordered function. Their work was supported by the subsequent observations of McCræ and Morris[6] in celiacs and by Black *et al*[37,38] on sprue in adults, all of which pointed to the conclusion that regardless of stooling, the administration of fat in steatorrhea improved fat absorption.

There has, however, been little direct evidence with which to answer the two leading questions involved: (1) what is the effect of feeding on absorption of the food itself and of other substances and (2) how does oral feeding affect the duration of the digestive disorder? If feeding increases the net loss of caloric food or of water and electrolyte or if it delays recovery, it is contraindicated, and if it does none of these things and favors absorption it would seem to be indicated. The studies of Chung[39] on infantile diarrhea, carried out at different levels of food intake failed to reveal any "washing out" of minerals or other foodstuffs caused by food administration, the amount of each foodstuff absorbed—whether calorigenic foodstuff, mineral or water—was found to be roughly proportional to the intake. The administration of food increased stool volume and stooling but in every instance, *and for every food ingredient studied net absorption* was either increased or loss was decreased. A study designed to evaluate the effect of feeding on the duration of infantile diarrhea was made by Chung and Viscorova[40] who treated alternate cases (*a*) by a conventional plan of initial starvation with a gradual resumption of food and (*b*) by offering full caloric feeding from the start. The duration of the disorder was found to be identical in the two groups, indicating that the duration of the disturbance is not influenced by the feeding. Similar observations have been made by others.

A series of studies of various forms *of steatorrhea*—celiac disease,[41] cystic fibrosis of the pancreas,[41] biliary atresia[4] and steatorrhea of prematurity[43]—was carried out by the group at New York University with a view to determining the effect of varying fat intakes. Similar observations on the steatorrhea of kwashiorkor were made by Gomez *et al* in Mexico.[43] Although the stool fat output increased with increasing fat intake, fat absorption was correspondingly increased and only clinical benefit was observed. The conclusion drawn from these studies was that intestinal intolerance in these states was not induced or indeed affected in any way by the administration of the poorly tolerated foodstuff. The increased stooling was interpreted as a *demonstration of existing intolerance* rather than as a relapse. These recent observations serve to support the views expressed in former years by Dubois,[34] Schick,[35] Park[44] and others and would seem to point to a more liberal oral feeding policy than has generally prevailed. It is of course quite possible, particularly in the chronic disorders, to feed these patients satisfactorily without using the poorly tolerated foodstuff to any great extent. It is, however, not necessary to do so, nor should the conclusion be hastily drawn that relapses when they occur are due to breaches of a prescribed diet. *In celiac disease in particular* such untoward events occur quite irrespective of the diet employed. The idea of "food intoxication" once widely held is now largely abandoned. It is now believed that the manifestations of "food intoxication" accompany-

ing a digestive upset are not caused by food but by dehydration associated with electrolyte losses and derangements of electrolyte metabolism

The Allergic Infant —Food allergy presents a special problem in infant feeding It may be observed even in the breast fed infant Hypersensitivity to the natural proteins of the mother's own milk has not been observed, but in rare instances[45] proteins ingested by the mother find their way unsplit into the milk in biological traces and when the sensitivity of the infant is extreme, they produce symptoms The mother herself may not be sensitive to the offending protein Elimination of the particular food from the maternal diet is followed by the disappearance of the symptoms

Hypersensitivity to one of the proteins of cow's milk—usually lactalbumin —is somewhat more frequently encountered and may be found in all degrees of severity Idiosyncrasy of an extreme degree is rare, but very dramatic in its manifestations A single drop of cow's milk may within a few minutes lead to urticaria, asthma acute gastro-intestinal symptoms, and shock of alarming proportions Fatalities have been reported In these circumstances the elimination of cow's milk from the diet must be scrupulously done Goat's milk is often well tolerated by these infants, but at times there is sensitivity to this also and a milk free diet must be given Such extreme sensitivity is not permanent By means of desensitization procedures in which small graded non-reactive doses are given a complete tolerance can be established though this may require a year or more

Lesser grades of food intolerance—sometimes to milk, eggs, wheat or other protein foods—are also recognized, the symptoms are usually gastro intestinal or cutaneous (usually urticaria) and they develop less promptly than in the extreme cases Rubin[46] and others[47] have reported acute diarrheas due to milk allergy in the newborn period, usually the symptoms are less acute Subjecting milk to autoclaving temperatures often denatures the lactalbumin to such an extent that it can be tolerated and a milk-free diet is not required In older subjects the celiac syndrome has been related by several investigators to intestinal allergy to wheat gluten [48]

Aside from the clearly demonstrable cases of allergy there is a wide zone in which respiratory, digestive and cutaneous manifestations are not so clearly related to allergy In this area, it is the opinion of this writer that the diagnosis of food allergy is often uncritically made and food unnecessarily restricted with resulting detriment to the patient It should be appreciated that a positive skin test in not synonymous with clinical allergy, such tests are frequently encountered in normal subjects Elimination tests —in the case of food allergy elimination diets—are needed to establish the diagnosis Only when the symptoms can be made to disappear on removal of the dietary antigen and to recur when it is restored to the diet, *other factors remaining constant* is one justified in assuming a causal relationship In the writer's experience, it is only in the exceptional case of digestive disturbance in early life that the diagnosis of allergy can be sustained by an environmental test It is also a mistaken notion that a child's distaste for a particular food such as spinach indicates that he is allergic to it An article of food to which a patient is hypersensitive is as a rule eaten with enthusiasm, even when—as in older subjects—its relation to forthcoming symptoms is known

The construction of a complete elimination diet free from all antigenic protein has been solved by a preparation in which all nitrogen is supplied in the form of amino acids and non-antigenic polypeptides The suspected food or foods can be added to this one at a time for diagnostic purposes When cow's milk allergy is demonstrated there are now many milk-free feedings that are available, complete feedings based on meat or soybean protein may be employed as well as the amino acid digest (see Chapter 27)

Some allergic patients appear to be benefited by a reduction in the carbohydrate of the diet for which fat is substituted The underlying mechanism is not clearly understood but appears to be related to a loss of fluid, chiefly extracellular, which occurs under these circumstances and which limits inflammatory reactions

The Premature Infant —The premature infant presents peculiar nutritional problems His caloric requirements are high, he absorbs certain foodstuffs—notably fats and fat soluble vitamins poorly He is known to have a greater need for vitamin C than the mature infant and it seems not unlikely that other special nutritive requirements exist He often regurgitates and aspirates his food with serious consequences It is in the smallest premature infants that these difficulties are more often encountered The small premature infant is born with negligible reserves of body fat and is poorly equipped to withstand caloric deprivation, yet it is often impossible to feed him maintenance diets for some days, one must proceed cautiously

The basal energy requirement of the premature is as high and perhaps higher than that of the full term infant and his growth rate is more rapid, the caloric loss in the excreta—largely unabsorbed fat—is also greater These are, however, partly compensated for by the low activity of these infants, so that the total caloric requirement is only moderately elevated Most of these infants will gain well on 125 calories per kg , some on less than this

The composition of the premature infant s feeding has been a controversial matter In years past breast milk has been regarded as the ideal food and the results with it appeared to be satisfactory The avidity with which these infants retain protein[49] however suggested that the low protein content of breast milk might be suboptimal for these infants The question still unsettled Higher protein intakes than that of breast milk will lead to increased nitrogen retention but whether or not this is advantageous is questionable

By and large premature infants absorb fat poorly although this steatorrhea is not apparent clinically Tidwell and Holt[50] showed that it could be substantially reduced by substituting more unsaturated fats for butter in the feeding Low fat feedings have been advised[51] on the ground that the more completely absorbed foodstuffs should be preferred in order to reduce the food intake to the minimum The validity of this procedure has been challenged by others who point out that because of its higher caloric yield a gram of ingested fat still provides more absorbable calories than a gram of protein or carbohydrate unless the absorption falls as low as 40 per cent which is rarely the case in the premature infant hence an economy of food intake is not achieved by avoiding fat Unabsorbed fat in the intes

time appears to be completely innocuous Morales *et al* [43] have also shown the interesting fact that the percentage of fat absorbed by the premature remains relatively constant regardless of the intake They were able to increase the total fat absorbed by increasing the fat intake without untoward effects, thereby achieving figures for total fat absorption comparable to those of full term infants This same principle has been applied for some time in the case of the fat-soluble vitamins which, like fat, are poorly absorbed, the absorption defect is met by increasing the intake

Premature infants have a peculiar need for vitamin C, particularly when relatively high protein feedings are given Levine and Gordon[5] demonstrated that unless this vitamin was generously supplied a characteristic defect of aromatic amino acid metabolism appeared with the excretion of so-called tyrosyl compounds (hydroxyphenyllactic acid and hydroxyphenylpyruvic acid) in the urine

In summary, the feeding of the premature infant should provide, as soon as this can be tolerated, a caloric intake of 125 calories per kg This can be accomplished satisfactorily by cow's milk mixtures as well as by breast milk The defect of fat absorption can be overcome in several ways by giving more protein and carbohydrate, by giving more fat or by giving a more readily absorbable fat An increased requirement of fat soluble vitamins is best established for vitamin D of which the intake should be no less than 2000 international units per day Single dose therapy of 300,000 units has also proved safe and effective A daily supplement of 100 mg ascorbic acid given for the early weeks is adequate to control tyrosyluria even on a relatively high protein intake Peculiarities of the mineral requirements of the premature infant are not known to exist Although the so-called anemia of prematurity[53] is a common event, this appears to differ in no sense from the physiologic anemia of the newborn and early infancy The administration of an iron supplement usually fails to influence this anemia prior to the third month

The feeding of premature infants is rendered difficult by their imperfectly developed reflexes Sucking and swallowing are often imperfectly performed by the small premature, who must in consequence be tube fed A small rubber catheter introduced at mealtime was formerly in general use, but in recent years this has largely been replaced by a small polyethylene catheter[54] which can be left in place continuously Regurgitation of food presents a greater danger of aspiration in the premature than in the mature infant, because the coughing reflex is often imperfectly developed The use of a continuous oral drip helps to reduce the volume of food in the stomach at any one time and thereby minimizes the risk of aspiration

Feeding Problems of Older Children —These are largely psychologic in origin *Anorexia* is an exceedingly common condition which is said to occur in nearly 50 per cent of American homes The difficulty usually arises from rigid ideas on the part of the parents or perhaps the grandparents as to what the child should eat and more particularly regarding the quantity he should eat, these being at variance with the child's appetite Coaxing and forcing of food effectively destroy the appetite and a vicious cycle is started In some instances this situation leads to psychogenic vomiting Often the child learns to capitalize on the concern of the parents regarding

his nutrition He enjoys being the center of attention and may hold out for special privileges in return for eating The therapy is simple, but sometimes difficult to carry out in a home where there are opinionated adults It is to set before the child a well balanced diet sweets being withheld until protein foods are eaten Comments on the desirability of eating are withheld and after a limited time—no longer than twenty minutes—the meal, if uneaten, is quietly removed, no food being offered until the next meal, when a similar procedure is followed A few strong-willed children will resist until the third day, but most of them will become hungry and capitulate before this, often eating ravenously foods which before they were unwilling to touch

Pica —The eating of dirt or of any inedible material though uncommon, presents a serious problem Its cause is not understood The theory that the habit starts from an effort to compensate for some dietary deficiency is not established in man, although this has been observed in experimental animals The habit is not dependent on mental defect, though defective children often practice it nor can it be correlated with other mental traits The danger from the ingestion of toxic substances is a serious one the most frequent difficulty being from the ingestion of lead from paint or plaster The habit may be difficult to break and requires careful supervision

With a few notable exceptions such as pica certain acutely ill infants certain mental defectives and a few situations of bad conditioning the appetite of the infant remains an excellent guide to his dietary needs, a far better one than is generally supposed The observations of Clara Davis[5] in which a group of normal infants were allowed to select their own diet from eight months of age onward for several years bear eloquent testimony to this fact Marked irregularities in the intake of particular foods were observed—a single food often being ingested in large quantities for a time but such dietary enthusiasms corrected themselves and over a long period the intake proved to be a balanced one the health record of these children being impressive It is unfortunate that sweets were not included in this classic study for there is other evidence that a "sweet tooth," if uninhibited, tends to correct itself in time

Unsolved Problems of Infant Nutrition —In spite of the notable advances in infant feeding made during the past half century, there are many nutritional problems contributing heavily to infant mortality and morbidity which remain unsolved *Frank nutritional failure* is still responsible for most of the deaths in infantile diarrhea Uncertainty still prevails as to the cause of many of these diarrheas Undiscovered microbial agents—producing enteral or parenteral infection—for which no specific therapy is available are doubtless responsible for many of these, their discovery is important A knowledge of the mechanism whereby an infection—enteral or parenteral—damages the assimilatory mechanisms of the intestine would be invaluable A knowledge of the steps involved in assimilatory mechanisms of the enzymes and co-enzymes concerned might make it possible to restore function even if the damaging agent could not be eliminated A perfect parenteral feeding would eliminate the immediate need of the digestive tract our present materials have well recognized imperfections

The largest infant mortality problem that of the smallest premature

infants, may well be due to nutritional failure Obvious causes of death are not found at autopsy and the diagnosis of physiologic immaturity is used to cloak our ignorance A more precise definition of immaturity in terms of defective tissue enzymes and co-enzymes might lead the way to replacement of some of the latter at any rate It is quite possible that the small premature infant needs a variety of accessory substances which the mature infant can manufacture for himself Their discovery might permit these subjects to survive without difficulty

Finally it is possible that many diverse diseases of known and unknown origin may exert baneful effects upon intermediate metabolism that are as yet unsuspected Accessory cofactors—unessential for the normal individual but essential for the disease state—remain to be discovered

NUTRITION IN ADOLESCENCE

The nutritional requirements of the adolescent are conditioned primarily by the *puberlal growth* spurt During this period, which in the individual child may be much more striking than average figures indicate, there is an increase in the apparent basal metabolic requirement which, as pointed out includes the growth requirement There is also an increased demand for calories and for nitrogen The increased caloric need is ordinarily reflected in the appetite Unless additional food is provided at mealtime the individual makes it up by eating between meals Exceptionally, the increase in appetite is inadequate and one observes a spindly individual who compensates for his or her increased caloric need by taking little exercise Figures collected by Gephart[56] for the caloric consumption of boys at boarding school were surprisingly large—much of this being consumed outside the dining room

The need for additional nitrogen at the time of the pubertal growth spurt has been stressed particularly by Johnston[57] The additional caloric need and nitrogen need are roughly proportional However, the increase in calories is too often supplied by carbohydrate alone Failure to meet the additional requirement for protein at this time is believed to be an important cause of loss of resistance to infections, particularly tuberculosis The loss of resistance at this time of life is seen particularly in the female whose growth spurt is more rapid, though less prolonged (Fig 74) Factors other than nutrition may, however, have some influence on loss of resistance such as the hormonal changes occurring at this time The practical consideration would seem to be the maintenance of a generous level of protein intake with the first evidences of puberty The maintenance of an adequate diet is often difficult in girls who often attempt to achieve artificial standards of slimness by ill-advised dietary restrictions Observations by Gardiner[58] suggest that the progression of myopia in growing children and adolescents may be related to their protein intake Some evidence was obtained that its progress could be retarded by an animal protein supplement

An extreme form of malnutrition, *anorexia nervosa*, is seen particularly in adolescence, although not confined to that time of life The term implies that this is a neurosis and there is no question that this is the explanation of the majority of cases, in whom a psychologic disturbance is often very

apparent We are not, however, inclined to accept the view that all non-fatal cases exhibiting such extreme anorexia and malnutrition should be regarded as neuroses in contrast to Simmonds' disease, where the syndrome is brought about by total destruction of the pituitary There is evidence for the existence of transitory or incomplete pituitary lesions which may induce this picture Such cases have been observed postpartum (Sheehan s syndrome) and it may be that the endocrine changes at puberty induce similar changes Such extreme forms of anorexia and malnutrition require expert psychotherapy but forced feeding is at times necessary

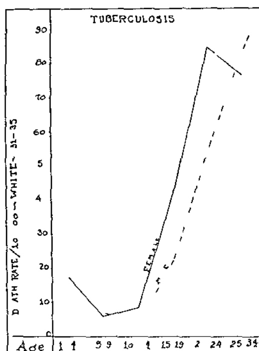


Fig 74 —Mortality rates in tuberculosis 1931–1935 Note the sharp rise in adolescence the increase occurring first in the female corresponding with the sex differences in pubertal phenomena (J A Johnston *Nutritional Studies in Adolescent Girls and Their Relation to Tuberculosis* courtesy of Charles C Thomas)

Obesity, although seen at all ages, may present a particular problem in the adolescent The adolescent girl has often been somewhat obese throughout childhood In many, self-consciousness and vanity coming with puberty will correct the situation, but in others there develops an attitude of defeatism There is withdrawal from social activities and sports and more indulgence in eating as a solace—a vicious cycle The same factors operate at times in the male The dietary management of obesity is discussed elsewhere in this volume (Chapter 30A) but the psychologic factors seen particularly during the adolescent period must not be overlooked

The problem of *simple goiter* or adolescent goiter is related to diet at this time of life The classical work of Marine and his co-workers[59] served

to relate this condition to a suboptimal intake of iodine The demand for thyroid hormone is increased at the time of puberty and in the presence of an iodine shortage the gland responds by simple hypertrophy The evidence cited by Marine *et al* consisted of the demonstration of low iodine in the soil areas where adolescent goiter was more prevalent and of a reduction of goiter when the iodine intake was increased Exception to this concept has been taken by Greenwald[69] who points to a number of discrepancies in the iodine content of the soil and the incidence of goiter, and particularly to variations in the incidence of goiter in the same locality from time to time Goitrogenic substances in foods and drugs may perhaps play a role in the incidence of this disorder The beneficial effect of iodine is, however, a fact beyond question, both prophylactically and therapeutically (see pp 275 and 286) Endemic goiter is seen particularly in isolated communities, usually in mountainous regions some distance from the sea The development of transportation invariably results in a sharp decrease in its incidence Food with a higher iodine content begins to come in from other places and there is a greater tendency for the inhabitants themselves to travel The problem of goiter is discussed elsewhere in this volume

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Chapter 36

Nutrition in the Aged

By Donald M Watkin and Edward J Stieglitz

The basic requirements for satisfactory human nutrition and metabolism are fundamentally similar throughout the life span However, the processes of aging induce many changes The period of senescence or involution thus presents special nutritional problems These are not as conspicuous or as well understood as the specific requirements peculiar to infancy and childhood, where growth introduces significant variables into nutrition Nevertheless, just as the child is not merely "the little man" but presents nutritional chemical structural, functional, immunologic and physiologic attributes characteristic of his age or phase of development, the aged person is not the same individual merely a "little older" The consequences of aging are more obviously manifest at the beginning and near the end of the life span, though *the processes of aging are continuous from conception until death*

Geriatric medicine[1] can not be rigidly and arbitrarily limited to the so called aged, for there are no sharp distinctions between the various phases of maturation and involution The answer to the simple question 'when is a man aged?' will vary greatly with the age of the one who replies It has been said "old is ten years more than your age" Geriatric medicine is not limited to the senile such limitation would render only disservice, and imply that palliation of long standing irrevocable and irreversible deterioration was the only therapeutic objective available Geriatric medicine is concerned with aging men and women as well as those already aged It is obvious that *far more can be accomplished for senescents than for those already senile* In many respects the two decades from forty to sixty years of age are the most significant It is during, or even prior to *these years that the future health of the aging and aged is determined* The application of knowledge concerning nutrition, to realize its full potentialities must be largely anticipatory or preventive[2]

Nutrition is more than diet There is considerable spread between the ingestion of foodstuffs and the utilization of vital nutritional elements by parenchymal cells It is the *cells* of the body which must be nourished Nutrition involves not only ingestion of adequate and balanced quantities of all necessary nutritive elements, but also their digestion in the alimentary canal, absorption, transport to the tissue cells and their cellular utilization for both anabolic and catabolic purposes Also included in proper or optimal nutrition is the effective removal of metabolic debris *Nutritional impairment may be consequent to interference with proper processing at any point in this chain* The tissue culture studies of Alexis Carrel revealed that cells appear to be essentially immortal *if maintained in an optimal*

nutritional medium This included the removal of noxious metabolic products at frequent intervals

As parenchymal cells exist in an internal milieu of interstitial fluids and a formed matrix, cellular nutrition is affected greatly by fibrotic changes, and/or hyalinization of the matrix, desiccation edema and the like

Impaired cellular nutrition may result from one or more of several factors

(1) Inadequate nutritional supply (dietary deficiencies)
(2) Excessive nutritional supply
(3) Impaired digestion
(4) Incompetent absorption
(5) Inefficient distribution (circulatory impairments)
(6) Ineffective utilization (hypo-insulinism asphyxia enzymatic defects)
(7) Inordinate accumulations of metabolic debris[3]

Malnutrition may thus be endogenous as well as exogenous Malnutrition includes excesses as well as deficiencies, a fact which, unfortunately, has been ignored by many If "normal" nutrition is taken as the average or "norm" of apparently well people (those not obviously ill), it may differ widely from optimum As health is relative and never absolute, the potentialities of an optimal nutritional status are still unrevealed Our present knowledge is inadequate for a comprehensive definition of optimal nutrition and/or optimal health

These endogenous factors in malnutrition are especially significant in geriatric clinical practice The feeding of the aged involves nourishing people with many impairments and limitations in functional capacities Nowhere is the relativity of health more manifest than in those whose age has permitted the accumulation of innumerable scars and injuries from the inevitable vicissitudes of existence The consequences of prior fatigues nutritional insults intoxications traumata and psychologic stresses are subtle insidious but accumulative It is impossible to separate those changes due to aging *per se* (mere passage of time) and those resulting from the many variable insults to which living exposes one These stresses and noxious experiences are truly unavoidable It is significant that they vary greatly between different individuals An increasing divergence must be expected with advancing age We are today what we are largely because of what we have experienced in our yesterdays The older we become the more yesterdays have affected us Thus it is essential that analysis of nutritional status and therapy by diet be highly individualized when applied to older persons

Geriatric nutrition is affected both by certain characteristics inherent in aging and aged individuals and by several generic characteristics peculiar to the disorders common among the elderly These significant elements can be considered separately

CHARACTERISTICS OF THE AGED AFFECTING THEIR NUTRITION

As individuals age they accumulate the subtle and insidious scars of prior injuries derived from many sources The immediate detriments may

or may not be apparent, frequently they are not But the cumulative effects can be of considerable moment These prior, silent and often wholly asymptomatic depreciations often become acutely exacerbated and first manifest when an acute illness produces stress It is in this connection that geriatric medicine stands in sharp contrast to pediatrics The pediatrician has the right to assume that prior to an acute illness the child is fundamentally well and that all the symptoms and signs observed are due to the acute disorder In geriatric medicine we must assume exactly the opposite that prior to an acute illness the patient was not fully healthy and that many of the evidences of disturbed function may be due to pre-existent conditions These pre-existent factors are often related to previous malnutrition The cumulative effects of minor dietary defects of long duration may logically produce minor and ill-defined deficiency states in the later years

It must not be assumed, however, that senescence implies only decline Where some functional reserves depreciate, others are improved The rate and degree of change in various structures and capacities varies considerably in different individuals and in different systems in the same individual It is characteristic that in older people the phenomena of diseases, or reactions to conditions of stress and/or injury, are much less conspicuous than in young individuals In geriatric medicine we must be constantly alert to detect and interpret the significance of subtle and minor variations [1]

The changes of aging are (1) relative and often widely divergent from chronological age, (2) asymmetric, (3) asymptomatic until functional competence falls below the physiologic requirements, (4) slowly but persistently progressive These fundamental attributes must be kept in mind constantly

As nutrition involves the several processes of ingestion, absorption, metabolism nutrient transport and utilization it is appropriate to consider the changes induced by senescence as they involve these activities

Factors Affecting Ingestion —Loss of teeth obviously interferes with proper mastication An inability to chew properly may so reduce the tolerance to certain types of food that important items are automatically deleted from the diet This applies particularly to the normal sources of bulk such as fruits and vegetables Meats also are often avoided Ill-fitting dentures, atrophy of the jaws etc , may be the major factor in the genesis of constipation due to lack of bulk, or, if the patient persists in eating certain types of bulk producing foods despite failure to chew them properly the syndrome of "irritable bowel," with alternating diarrhea over-emptying of the colon and sigmoid, and constipation may result

In the elderly, the role of *habits* in determining health is particularly significant Habits good, bad or indifferent, are acquired and fixed by repetition over a period of time Duration is requisite, age is therefore a significant element in habit fixation Dietary habits are probably one of the greatest obstacles in the path toward optimal nutrition [4] Habits may last longer than life itself, for they may be transmitted from one generation to the other It is extremely doubtful, for example, whether obesity is primarily an inherited characteristic in the purely genetic, biologic sense The child who grows up in a family where the parents are obese by reason

of overeating acquires the habit of eating more than is desirable. Food prejudices are likewise usually acquired early in life, from family tastes and cultural environment. It is notable that the less knowledge of nutrition an individual has the more firm are his or her convictions based upon prejudice and habit. The longer habits have persisted the more deeply rooted and rigid they become.[5]

Occasionally one observes an aged patient who, because of faddism, prejudice or simple gustatory preference and self indulgence, has subsisted for many years on a diet simply outrageous to the scientific nutritionist, and yet is found to be in exceptionally robust health.

One such instance will suffice to illustrate: a man of eighty seven years, in remarkably good health, vigorous, alert, with a normal cardiovascular system and optimal hemoglobin content had lived over fifteen years on a diet consisting *solely* of bacon and pineapple juice because of his own peculiar theories. The fact that he had so limited his food supply was convincingly attested by his family, who brought the old gentleman to the physician because they felt he must be doing himself harm with his apparently inadequate diet. Instances such as this, though not common, should remind the clinician and laboratory scientist alike that there may be exceptions to the rules and that it may be wiser to listen carefully to the elderly patients and give *considerable weight to their prejudices, even though they seem illogical.*

It is wise not to insist upon abrupt changes in the habits of aged patients. Unwise habits can be modified slowly, but sudden and radical changes in the mode of life are physically upsetting and emotionally disturbing. Furthermore, if the advice regarding dietary habits is too restricted or too much at variance with the established mode of life, the patient will not follow the therapeutic suggestions and nothing whatever is accomplished.

Economic factors are often significant in the selection of a dietary by the elderly, particularly today. Flour and sugar are the cheapest foods. The tendency is for the older people to eat too much carbohydrate and not enough protein.[6] This tendency is further fostered by the ease with which packaged bakery goods, all ready to eat without further preparation, are obtainable. Elderly persons living alone, and there are truly millions of them in urban centers, are not sufficiently interested in eating to prepare proper meals. An old folk lore saying is particularly pertinent: "Old John would half-starve were there no woman to prepare his meals, old Nellie would starve if she had no one to share her cooking." The element of "aloneness" must never be ignored in an analysis of the genesis of dietary habits. Another factor in the undesirably high proportion of calories derived from bakery goods in the elderly is the fact that fresh bread is easy to eat, requires little chewing and is always liberally supplied in institutional dietaries because of its cheapness. McCay has observed that the per capita consumption of bread in the State Mental Hospitals of New York State exceeded that of the young men in Navy training camps.[7]

The ease with which food is consumed and digested also affects the selection of foods by the elderly. Appetite is variable in the aged. Long and continued habitual anxiety may lead to either a serious anorexia or to

excessive consumption of foods, with obesity as a consequence Anorexia is not uncommon when morale is low because of long distressing illness and disablement In anorexia, small frequent feedings are often much better tolerated than larger meals Where appetite is poor, one of the most important considerations is that the food supplied be "easy to eat" Patients will sometimes refuse a delicacy such as a squab but eat a simple hamburger, because the latter is already ground and requires a minimum amount of effort for consumption Such individuals are not interested enough in eating to take the trouble to pick the meat off the squab Considerable food can be introduced in beverage form, if the appetite is very poor Sometimes it is useful to increase the intake of salt in the food of the anorexic patient and thus increase thirst which is used to encourage the consumption of nourishing beverages This procedure is, of course, contraindicated by the presence of edema, cardiac incompetence, hypertensive arterial disease or nephritis (see Chapters 24 and 26)

Obesity is rarely a problem of the truly aged It is, however, a far more frequent and serious problem in the middle years of senescence[6] The obese rarely survive to great age The experimental studies of McCay[8,9] have convincingly demonstrated a close correlation between enhanced longevity and quantitative restriction in diets of experimental animals In man the relation between obesity and reduced longevity has been thoroughly and repeatedly validated by large actuarial studies by insurance companies

Factors Affecting Digestion and Absorption —Secretion of digestive enzymes and hydrochloric acid in the stomach and the intestinal canal diminishes with age Atrophy of and degeneration of cells in the salivary glands together with a decreased saliva production and ability to digest starch have been observed in individuals over 60[10,11,12,13] The incidence of achlorhydria in similar age groups has ranged in various reports from 9 8 to 35 4 per cent[14,15,16,17,18] Trypsin and pepsin secretions are diminished Amylolytic and lipolytic activity are also decreased although less than proteolytic[19] The actual volume of all alimentary secretions is lessened Therefore, considerable impairment in the digestion and absorption of nutrients might be anticipated[0] However, studies employing the metabolic balance technique[1,21] and test meals of protein labelled with radioiodine have demonstrated protein absorption to be as good in the aged as in the young Chronic cholecystitis and impaired hepatic function may interfere with the utilization of fat Impaired fat absorption has been reported[23] Fats often induce considerable flatulence and discomfort in the elderly and thus may be spontaneously avoided[4] Under such circumstances dietary deficiencies of fat soluble vitamins are not unusual Absorption of vitamin A, however, is not impaired in the aged[5,26] Vitamin B_1 absorption in the aged following administration of the radiocobalt labelled vitamin varies widely among individuals[8] but has been reported to be similar to that observed in young adults[8,29,30]

Constipation is a frequent complaint among the elderly although its prevalence objectively is not greater than among young adults[31,32] With aging muscular atrophy of the colon sigmoid and rectum may contribute to constipation Inhibition of the evacuation reflex carried over the

sacropelvic parasympathetic nerves is another contributing factor[14] A diminished secretion of mucus, which normally serves as a lubricant in the lower intestines, *increases the tendency to constipation* However, the major factor in constipation in the aged is unwise dietary habits An inadequate intake of water is the most common deficiency insufficient bulk is *the second most important factor It must be remembered, and the* patients instructed that one of the functions of the colon is to reabsorb water from the liquid contents entering the cecum from the small bowel *If the body is short of water, reabsorption will unduly dry the fecal mass* and lead to hard inspissated stools which may become impacted Probably the optimal fluid intake is such that approximately 1500 cc of urine are secreted per *twenty-four hours* Except under *conditions of excess* loss by perspiration this usually requires an intake of about 2 liters One must be cautious not to overdo the administration of bulk producing medication *such as Saraka, Serutan psyllium seed agar-agar or methyl cellulose* because massive rectal impaction may result The re-education of the atonic bowel which has depended upon the irritation of cathartics for *many years must be gradual and carefully controlled*[33]

Diverticulosis of the colon and sigmoid is extremely common in the later years the incidence in one study being reported as 34 6 per cent[14] Many times *the diverticula are wholly symptomless and are discovered coincidentally* in diagnostic studies pointed at other gastrointestinal disorders Recurrent episodes of inflammatory reaction diverticulitis are common and must always be *considered as a potential threat Only in a very few* instances of recurrent diverticulitis does the situation become serious usually the attacks are more a nuisance than a serious menace Nevertheless *the possibility of perforation peritonitis and the development of* intestinal vaginal or vesicle fistulae must be kept in mind[33] It is thus wise for the aged to avoid foods containing seeds or hard indigestible fragments such as nuts berries *whole tomatoes (strained tomatoes are not* only permissible but desirable because of the vitamin C content) bran and the like These particles are likely to be entrapped in the diverticula and *initiate the inflammatory reaction of acute diverticulitis*

Flatulence may be due to many factors Air swallowing is common especially among neurotic individuals Inadequate secretion of digestive enzymes biliary insufficiency and imbalance between carbohydrate and protein intake are common sources of undue flatulence The correction of this complaint involves no different concepts than the treatment of flatulence in younger patients

Metabolic Factors Affecting Nutrition in the Aged —As previously mentioned nutrition involves more than ingestion digestion and absorption Utilization *of nutrients and their transportation to the parenchymal cells* must be considered With normal aging there is a gradual diminution in homeostatic efficiency Disease frequently accentuates this depreciation Tolerance *for any and all forms of stress is diminished* Older individuals do not adjust as well as younger adults to extremes of temperature rapid intake of fluids dehydration, starvation or gluttony ingestion of alkaline or acid producing foods, etc The early lowering of the efficiency of

homeostatic mechanisms is revealed only by observation under conditions of stress

As age progresses more and more older people respond with a diabetic like curve to the glucose tolerance test Too rapid administration of glucose, either orally or parenterally, is not well tolerated by the aged Likewise, the older individual does not tolerate a lowered blood sugar, whether the result of starvation or hyper-insulinism Soon after the introduction of insulin into the management of diabetes mellitus it was observed that elderly diabetics when precisely controlled to maintain a "normal" blood sugar continuously, frequently developed circulatory difficulties A relatively low blood sugar (even if higher than the fasting normal levels of young adults) may induce episodes of acute angina pectoris[34] Glucose is a major source of cardiac energy in the recently fed individual[35–37] In the fasting individual however, unesterified fatty acid (UFA) is the major source of cardiac energy requirements[38 39 40] The desirability of maintaining a relative hyperglycemia (120–180 mg per cent) in patients with congestive cardiac failure, particularly elderly patients, has been stressed[35] The administration of small quantities of readily absorbed carbohydrates at frequent intervals (such as honey or syrup, 1 or 2 ounces every two hours) may be significant to recovery from congestive failure[41]

Pyruvate is involved in glucose utilization Since cocarboxylase, which is derived from thiamin is essential to the normal utilization of pyruvate, thiamin deficiency even of minor degree, affects cardiac reserve adversely[4] There is a close relationship between glucose metabolism and blood potassium content[43] When the supply of glucose as a source of cardiac energy is inadequate the myocardium derives its energy from UFA[38 39 40] Hence if the heart is to utilize glucose, the desirability of which has been mentioned[41] a sufficiency of glucose adequate oxygen and enough insulin to catalyze the reaction are necessary

The policy of "a little, often" is a basic principle of dietotherapy of the aged, both those relatively well and those acutely ill It is applicable to fluid ingestion as well as other nutrients In hospitals and institutions where personnel problems determine mealtimes and the evening meal is often served at about 5 00 P M or even earlier, the long interval until breakfast should be broken by a bedtime snack[44] It is important to prevent nocturnal relative hypoglycemia and/or dehydration in the elderly[34 44]

The aged because of the depreciation in their renal functional reserves develop an increasing inability to handle excesses of alkali, excesses of acids are more efficiently disposed of because the normal physiologic mechanisms of the organism are prepared for the riddance from the body of acid substances Sippy ulcer management with sodium bicarbonate not infrequently induced alkalosis in elderly patients[46] Alkalies should therefore be prescribed with caution The recent renewed vogue of rigid salt restriction in the management of hypertension,[47–50] and mild pedal edema of circulatory origin and/or the administration of cation exchange resins[41 51] has increased the frequency of the acute low salt syndrome Salt depletion is dangerous in the elderly[5] It must be watched for and anticipated, especially in those who restrict their salt intake and most particularly

during hot weather, fever and after surgical operations when the chloride loss by perspiration may readily exceed that ingested.[1,53]

The ill consequences of hypoproteinemia in causing edema, poor wound healing, retarded bone repair, decreased resistance to infection, slowed hematopoiesis, etc., are more frequent in older persons.[54] The maintenance of plasma protein is desirable.[55,56] This is particularly urgent in both preoperative and post-operative management of the elderly patients[53] (see Chapter 32).

Although conflicting data on the protein requirement of the aged have been presented, an evaluation of available evidence implies that an adequately balanced diet containing one gm. protein per kg. satisfies the requirement of the healthy.[57] Individual problems, however, call for special solutions tailored to the conditions at hand. Several new approaches to the problem are providing additional information on protein absorption and over-all and intermediary metabolism. The *amino acid requirements* of the aged are receiving considerable attention. Some evidence suggests *that older men have a greater requirement than young adults or that the* supplementary nitrogen accompanying the essential amino acids may not be readily available to them for synthesis of nonessential amino acids as in the case of young adults.[58] Other studies have suggested a methionine deficiency in the self selected diets of older women.[59] Still others have suggested the desirability of diets high in animal protein and have demonstrated improved nitrogen retention in aged subjects after supplementation of diets high in cereal protein with lysine.[60]

The one, and therefore notable, exception to the constancy of physiologic constants with advancing age is decline in the rate of metabolism. This unique change is not universal for all mammalian species; it does not occur in dogs or rats. Recent studies[57,61,6] suggest that the decline in oxygen consumption with age reflects a change in body composition, not a decrease in the average rate of oxygen uptake per unit of tissue after maturity. Estimations of body water volume and distribution using antipyrine, Evans-Blue (T-1824 dye) and thiocyanate revealed a significant diminution in total body water with increasing age but no similar change in plasma volume or thiocyanate space. Basal oxygen consumption per unit of total body water or per unit of "intracellular fluid" (antipyrine space minus thiocyanate space) did not diminish with increasing age. Oxygen consumption per liter of thiocyanate space did diminish as did oxygen consumption per unit of surface area or body weight. This evidence suggests that the decrease in metabolic rate with age is directly related to the amount of functioning protoplasm remaining in the body and that this gradually diminishes during the aging process. Prevention of the decrease in metabolic rate becomes therefore a matter of the prevention of the atrophy and death of cells. These conclusions do not invalidate the concept that the aging human organism consumes less oxygen and therefore expends less and less calories per unit of time and total body weight as it ages. It still remains to be proven that this decline in oxygen consumption with advancing age is teleologically desirable. Just because it occurs in the majority of individuals is not convincing evidence that the reduction is optimal. For example, it is well known that the great majority of people tend to

gain weight after maturity, but this gain affects longevity and health adversely

From the viewpoint of geriatric nutrition the diminution of caloric requirements associated with the declining metabolic rate with age is of considerable pragmatic significance As habits of eating often persist unaltered though the energy expenditure is gradually but considerably reduced, it is not surprising that obesity is such a common problem during the middle years of senescence Furthermore, *thyroid activity* is directly related to cholesterol metabolism It is highly probable that hypothyroidism, even if relatively minor, may be a significant factor in the genesis of atherosclerosis [56,63,64] Added to the hormonal factors is the element of diminishing physical activity [65] The potentialities of more nearly optimal nutrition in the anticipation, prevention and retardation of cardiovascular (arteriosclerotic) disorders have been under investigation [66–75]

Aging brings about changes in mineral and electrolytic metabolism which affect *geriatric nutrition* As yet our knowledge in this area is but fragmentary there is much to be learned We know a little about calcium, iron phosphorus, sodium, potassium and chlorides The last three electrolytic factors have been discussed above in relation to the changes in homeostasis with aging Little is known about the need for greater (or perhaps lesser) requirements for iron with advanced age Microcytic anemias associated with poor iron intake from socio-economic reasons have improved on iron administration [76] It is clearly evident that the maintenance of a near optimal *hemoglobin content in the blood is essential to* well-being in later years This is particularly so when any circulatory impairment exists (an almost universal situation among the aged) Either arteriosclerotic narrowing of vessels supplying vital parenchymatous tissues such as the brain, or the relative ischemia distal to constricted arterioles in hypertensive disease, diminishes both the rate and volume of blood flow to the parenchyma and reduces the margin for increased effort Thus, if the *quantity* of blood is reduced, the *quality* thereof takes on even greater significance than in youth where deficiencies may be compensated for more readily by accelerated flow [1]

Osseous demineralization, with osteoporosis is a major problem in the aged, both in frequency and degree of disablement Many factors *are involved* Impairment of absorption, in part secondary to lowered gastric acidity and hepatic and pancreatic insufficiency, contributes An immediate result of these deficiencies is poor absorption of fats Experimental studies indicate that it is difficult to maintain calcium balance in old animals [86] *Fats promote* wastage of calcium in old age [87] Studies of the nutritional status and requirements of 100 women, forty to seventy-five years of age, reveal that the calcium requirements of older women are higher than standards proposed for adults [88,89] *In older men* there is some evidence that the calcium requirement is higher than for young adults [90] However other workers have concluded that in the absence of osteoporosis calcium metabolism is no different in *old than in young* men [91,92,93] In osteoporosis recent investigations[94,95] have suggested that increased calcium intake may induce calcium retention independently of protein retention which has been regarded by some as the exclusive *defect*

in osteoporosis[96] Others have shown a failure to store any appreciable amounts of calcium on high calcium diets despite markedly positive nitrogen and phosphorus balances[91] Stilbestrol has been shown to induce calcium retention in males with osteoporosis by what may be interpreted as a direct action on calcium itself[97] Stanolone administration at two levels of protein intake failed to increase calcium retention despite marked increases in nitrogen and phosphorus retention[1] Much additional work has been done on the role of protein intake and steroid hormone therapy as well as on the role of glycogen and glycogenolytic enzymes and parathyroid hormone[96 98–10]

Factors Affecting Transport —Ingested and digested nutrients are useless unless actually delivered to the tissue cells requiring them Transportation of absorbed food elements is often adversely affected by impairment of the circulation Cardiac inefficiency reduces the supply of oxygen to the tissue cells as well as interfering with removal of metabolic debris Oxygen inadequacy is a nutritional deficiency Arteriosclerosis is nearly universal in the aged, though the exceptions prove that age *per se* is a contributing factor rather than the primary factor in the genesis of arteriosclerosis That nutritional factors play a significant part in the causation of this common and most important disorder is unquestioned, though thus far there is much confusion of the interpretation of clinical and experimental observations[64] Fats and especially cholesterol, have been indicted Recent studies have minimized the importance of dietary cholesterol in atherogenesis and emphasized the role of dietary fat[77–80] Much discussion and some controversy have arisen over the mechanisms by which dietary fat influences serum cholesterol concentrations One group has suggested that these concentrations may be increased in technically developed areas of the world because of a deficiency in the modern diet of essential fatty acids[81] Others have presented evidence that serum cholesterol concentrations may be decreased by the isocaloric substitution of unsaturated for saturated fats in the diet[74 75] Still others have presented mathematical formulas relating changes in serum concentration of cholesterol to the total quantity of fat in the diet and indicating that an equal amount of saturated fat is twice as effective in increasing the serum cholesterol concentration as is unsaturated fat in decreasing it[73] All seem reasonably agreed that monoethenoid fatty acids are ineffective and that the polyethenoid fatty acids are more effective in reducing serum cholesterol concentrations in individuals with hypercholesterolemia than in those with average concentrations Corn oil among the unsaturated fats has a particularly marked serum cholesterol depressing effect The possibility that a nonlipid component in trace amounts may be the active ingredient reducing serum cholesterol concentrations has not been ruled out[74 82 83] The probability is high that all shades of opinion will prove to be at least partially correct[84] More definitive answers to numerous questions in this field will gradually appear from studies with glycerides synthesized from pure fatty acids[74] and with more general use of such techniques as gas liquid chromatography[85] A high fat intake in the diabetic contributes to the premature development of arteriosclerosis However diabetes is a general metabolic disorder arteriosclerosis and capillary changes are accelerated in diabetics even if maintained on a low fat regimen[104 105] (see Chapter 23)

Hypertensive arterial disease interferes with the nutrition of tissue cells. Distal to the obstruction of arteriolar constriction, the circulation is impaired. Capillary stasis creates local impairment of the oxygen supply. The greater the arteriolar constriction the poorer the capillary circulation, and the higher the arterial tension.[31, 41] Diminished capillary permeability may add to impaired renal efficiency in enhancing accumulation of detrimental metabolic débris in the tissue interstices. It is essential to remember that correction of defects in transport of nutrients *to* the cells and of metabolic débris *from* the cells is part of the problem of nutrition.

THE RELATION OF NUTRITION TO THE DISEASES MOST COMMON IN THE AGING AND THE AGED

Age confers no absolute immunity to any illness, the aging and the aged may have any disease seen in infants, children, or young adults. But a significant group of disorders, often loosely called "the degenerative diseases," increase sharply in frequency in later maturity and lead to most of the disability of later years.[1, 107, 108] *The term chronic progressive disorders* of later maturity, though more cumbersome than "degenerative diseases," is more definitive and accurate. The new growth of cancers, for example, is regenerative rather than degenerative. Included in these disorders are four major groups: circulatory disorders, metabolic disorders, neoplastic growths, and skeletal disorders. A greatly simplified classification follows:

A. Circulatory disorders
  1. Chronic infective myocardial disease
     (a) Rheumatic
     (b) Luetic cardiac and/or aortic
  2. Hypertensive arterial disease
  3. Arteriosclerosis
     (a) Cerebral: apoplexy
         dementia, amentia
         encephalopathy
     (b) Coronary: cardiac disease
     (c) Renal: chronic nephritis
     (d) Pancreatic: diabetes mellitus
     (e) Extremities: gangrene
         Buerger's disease

B. Metabolic disorders
  1. Diabetes mellitus
  2. Anemia
  3. Climacteric, female and male
  4. Gout

C. Neoplasms, all forms

D. Arthritides

Of these the first two groups, the circulatory and metabolic disorders, are preeminently important. They are so *intimately related* that attempts to separate the consequences into distinct and isolated disease entities are futile.

All these disorders have certain generic characteristics of great clinical and nutritional significance in geriatric medicine These generic attributes can be related to etiology and pathogenesis, onset and course

The *causation* of the chronic progressive diseases of later maturity is largely endogenous and cumulative They arise consequent to an accumulation of injuries from various sources The variable and inevitable vicissitudes of existence are contributing etiologic factors It is pertinent to emphasize that in no two individuals are these sources of injury, which are intrinsic with living, the same in character, severity or sequence Individualization and thoroughness of diagnostic study are twin essentials in geriatric medicine

The *onsets* of these disorders are silent and wholly asymptomatic for a long time often many years This latent silent period is of great importance for it is at this time that one may hope to accomplish the most in preventive therapeutics Later when obvious symptoms and signs have occurred, it often is too late to accomplish more than some retardation of progression or the maintenance of a *status quo* To be discovered early enough for these disorders to be amenable to maximal correction and control, they must be searched for An attitude of prevention and anticipation is requisite to successful accomplishment, it does not suffice to have hindsight to explain the pathogenesis of disease Foresight as to what is likely to occur and the recognition of subtle deviations and their potential significance are required for truly good anticipatory or constructive medicine

Another significant generic characteristic is that of *progressiveness* Though often slow (thirty years or more) progression is persistent and spontaneous remissions are at best but very transient Thus one may anticipate gradually increasing disability and long periods of relative invalidism from these chronic illnesses [109] The preventive aspects of chronic illness include the maintenance of as nearly as possible optimal nutrition in youth

Finally, many of *these disorders overlap* and more often than not co exist in the same person Their frequent coincidence, however, is not coincidental There is significant overlapping in etiologic factors, pathogenesis and consequences Such disorders as arteriosclerosis, diabetes mellitus, hypertrophic arthritis, hypertensive disease and the like are often thought of as precisely demarcated entities Actually they are not so separable They present a biologic unity in pathogenesis, in that all of them interfere with the nutrition of parenchymal cells It is significant that anemia contributes to the pathogenesis and perpetuation of hypertension, that hypothyroidism contributes to the resistance of anemia to nutritional therapy, and also to the genesis of atherosclerosis that diabetes mellitus (even if well controlled) exacerbates arteriosclerosis, that the achlorhydria of pernicious anemia affects the nutrition as a whole and that gout arteriosclerosis and renal impairment are related

The physician faced with the problem of diagnosis in senescent individuals must presuppose the presence of several disorders Even if the presenting illness is acute he must assume that there exist chronic impairments prior to the onset of the acute disease Thus he is routinely faced

with the problem of deciding which of the physical signs and subjective *symptoms are due to superimposed acute disease* and which to preexisting impairment of health

Lastly, it is typically characteristic of most of these chronic progressive disorders to *present only indirect subjective symptoms and physical signs* Arteriosclerosis, hypertension, thyroid dyscrasias, anemia, early cancer, and the like produce no symptoms *directly* attributable to the pathologic lesions of the disease There is no kinesthetic sense informing us of variations in the arterial tension, there is no awareness of arteriosclerosis or of hyperglycemia The consequences are *indirect* They arise from other structures than those primarily affected, largely because these disorders impair the nutrition of parenchymal tissues Thus the symptomatology is extremely variable For example, the symptoms of vascular disease may be cerebral (mental or organic), cardiac, visual or metabolic in character depending upon whether circulatory inadequacy is preeminently in the brain, the coronary circulation, the retinae or the pancreas The problems presented are not only complex but highly individualistically variable

The relation of these disorders to nutrition is reciprocal The diseases *contribute to impairment of cellular nutrition by interfering with absorption, transport and/or utilization* Malnutrition unquestionably contributes to the etiology, pathogenesis, perpetuation and progression of these disorders Obesity increases surgical risk[110] and predisposes to hypertension, diabetes, arthritis and atherosclerosis[111] Undernutrition contributes to anemia as well as specifically producing characteristic deficiency disorders[112]

SUMMARY

Both the sciences of nutrition and gerontology are advancing rapidly at present Our knowledge concerning the changing capacities and limitations which come with aging, and therefore the alterations in nutritional requirements, is in a state of flux With every increment in knowledge certain older concepts will require revision, for all human knowledge is but tentative because it is grossly incomplete However, awareness of ignorance should not prevent us from properly applying that which we know

The criteria of gross malnutrition are fairly well worked out Minimal requirements of most nutritional elements are known at least approximately But what constitutes *optimal* nutrition and the requirements therefor, are as yet largely a matter of conjecture In the light of present knowledge the following principles are essential to good nutrition for the aging and the aged

(1) *Moderation* —Excesses constitute malnutrition just as much as deficiencies

(2) *Liberal Fluid Intake*

(3) *Balance in Dietary* —Awareness of the potential asymmetries consequent to fixed habits alerts the physician to probable deficiencies, especially in protein, iron and calcium

(4) *Individualization* —Variations in physiology, requirements, tolerances and capacities increase with age

(5) *Gradual Modification of Dietary Habits* —The elderly can not tolerate abrupt changes if ambulatory, the patient will ignore rigid or unreasonable advice

(6) Recognition of the intimate reciprocal relationships between nutrition and the chronic progressive disorders of later maturity

(7) Attention focused upon the entity of the individual rather than upon his diseases The individual is indivisible, psyche and soma are one To ignore psychic factors is to fail to obtain maximal results from dietary therapy

(8) The primary objective is the construction of health to as near the optimum as possible, not merely to treat disease Anticipation and prevention are vastly more effective than repair of avoidable damage already induced Health is much more than the absence of disease

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Chapter 37

Food and Nutrition Relating to Work and Environmental Stress

By Maurice E Shils

NUTRITIONAL REQUIREMENTS FOR WORK

It may be stated at the outset that the overwhelming majority of male and female workers have nutritional requirements of the same order as those for individuals of the same sex and age in the general population Hence, the investigations establishing our present knowledge of human needs are applicable to industrial workers However, there is need for an examination of the possible influences on nutritional requirements of various activities and stresses imposed in various occupations, in order to know whether any significant changes occur that demand alterations in dietary practices A corollary question concerns the effect of variations in dietary composition on work performance

Calories —Measurement of energy needs during a variety of human activities have been based primarily on indirect calorimetry since the pioneer studies with a human calorimeter at the end of the last century There has been a recent renewal of interest in such measurements, in part due to the development of new and more convenient apparatus In addition, new data have been necessary since methods and amount of work in many industries and in agriculture have undergone a profound change with rapid advances in mechanization and specialization, and with shortening of the work week in technically advanced countries

Assessment of energy expenditure at a given task may be measured most reliably by indirect calorimetry during performance of the task If this technique is applied to each activity of daily living and the time spent on each activity is known, then the total caloric cost of the day can be estimated Earlier workers such as Voit, Atwater and others after them estimated energy expenditure by analyzing diet records—a procedure open to a number of errors, including errors in the measurement of consumption, variations from the tables of food composition, variations in efficiency of food utilization and, individual weight changes on given diets The use of data obtained from indirect calorimetry for generalization also involves the problem of transferring data from a small group to a large population or to an untested individual, however, its error should be smaller by far than the dietary method Using tables based on calorimetric estimates, Passmore and Durnin[1] consider the more recent estimates of individual daily energy expenditure to be accurate within 10 per cent

The development of a light weight portable respirometer[a, b] has greatly facilitated the obtaining of data on energy expenditure This unit measures

the volume of expired air directly and simultaneously diverts a small fraction (0 3 to 0 6%) into a rubber bladder for subsequent analysis Weighing less than 8 pounds, it has important practical advantage over the bulky Douglas bag which was used in earlier studies[2 – d 3 – 3]

Using this Kotranyi-Michaelis respirometer, Lehmann *et al* [d] in Dortmund carried out observations on German mining and industrial workers during the period 1940–1949 While actual measurements were made only at work, these investigators made assumptions for energy expenditures outside working time to obtain daily energy requirements More recent surveys made in Britain included indirect calorimetry and a complete recording of daily activities so that overall daily energy expenditures could be more accurately estimated One of these studies[3a] had as its subject coal miners and colliery clerks in Scotland

An excellent summary of these and many other studies has been presented by Passmore and Durnin [1] They have collected data from the literature and their own investigations on the energy expenditures in sleep, personal care walking, climbing running recreational activities, domestic and office work, and a large variety of laboring activities ranging from light to very heavy and including agriculture, lumbering and fishing as well as industrial work The reader is referred to specific activities listed in their tables for individual figures on energy expenditure

Numerous efforts have been made to grade physical effort as a basis for estimating caloric needs We may mention a few of these as points of reference

Burnet and Aykroyd[4] reporting for the Technical Commission of the Health Organization of the League of Nations in 1935 suggested an allowance of 2400 calories per day as adequate to meet the requirements of an adult male or female living an ordinary everyday life in a temperate climate and not engaged in manual work with the following supplements for muscular activity light work, up to 50 calories per hour of work moderate work, from 50 to 100 calories per hour of work hard work, from 100 to 200 calories per hour of work and very hard work 200 calories and over per hour or work Expressed in another way, work was graded as follows

Grade	*Cal/min*
Light	up to 2 6
Moderate	2 7–3 8
Hard	3 9–6 3
Very hard	6 4–up

These grades are based upon an intensity of work that is maintained as an average Dill[1b] expressed levels of work in terms of the ratio of work metabolism to basal metabolism and defined moderate work as that in the range where the work metabolism is 1 to 3 times basal metabolism, and hard work as that in the range of 3 to 8 times In the latter area lie most of the manual jobs in heavy industries building trades, mining and agriculture

During World War II the Food and Nutrition Board of the National Research Council considered the problem of the calorie requirements of industrial workers at the request of the War Food Administration, following

the demand for extra amounts of rationed foods by workers in heavy industry.[5a,5b] Recognizing the paucity of data on the requirements of occupational groups, the Board classified industrial workers into 4 categories for the purpose of differential allowances.

Of interest in this connection are the Reports of the Committee on Calorie Requirements of the Food and Agriculture Organization of the United Nations.[6a,6b] These present formulas for calculating the calorie requirements of populations and population groups by establishing "reference standards" for men and women and adjusting the requirements of individuals differing from the reference in age, body size, environmental temperature and activity. The mean calorie requirements of the reference men and women involved in a degree of activity corresponding to an occupation in light industry are 3200 and 2300 per day, respectively. The Food and Nutrition Board of the National Research Council in its 1953 revision of the Recommended Dietary Allowances adopted these references as a basis for calorie requirements. In its 1958 revision the Food and Nutrition Board retained this approach but modified some of the FAO reference conditions. Having knowledge of the characteristics of a population group with respect to distribution as to age, body size and climate and activity, estimates of the caloric needs of that population can be reached. Lehman, Muller and Spitzer[7d] recorded the energy needs of many hundreds of German workers in a large variety of occupations during the period 1940 to 1949. They estimated the over-all daily calorie requirements of German workers and suggested a range of probable caloric need for a given occupation. On the basis of their findings and of previous work, they classified hundreds of occupations into 1 of 10 groups of calorie requirements, ranging from 3/6 of basal metabolic rate (less than 2550 Cal.) up to 17/6 and higher (greater than 5000 Cal.).

Christensen[5c] suggested the following definitions of different grades of work:

Unduly heavy	—energy expenditure over 12.5 Cal/min
Very heavy	—energy expenditure over 10.0 Cal/min
Heavy	—energy expenditure over 7.5 Cal/min
Moderate	—energy expenditure over 5.0 Cal/min
Light	—energy expenditure over 2.5 Cal/min

This grading is based upon actual caloric cost in performing the work rather than upon an average including rest pauses and, for this reason, exceeds that proposed years ago by the League of Nations Committee.

Passmore and Durnin[1] are in agreement with Christensen's definitions on the basis of their own work and urge their introduction into general use.

The energy expenditures of each of Christensen's grades apply only to rates of work which are carried on continuously for periods of a few minutes and must be interspersed with rest pauses. Hence, these definitions need to be considered in relation to work capacity in order to give information on average daily rates of work. Lehman[3b] and Muller[3c] have considered this problem in the light of their studies on German workers. They set a figure of 4 Cal./min. net or 5 Cal./min. gross (*i.e.* including energy of basal metabolism) as the upper limit of energy available from foodstuff oxidation

and they term this value, the Endurance Limit. If more energy is needed anaerobic metabolism with accumulation of lactic acid results.

Work at 5 Cal/min gross for an 8 hour shift equals 2400 Cal and probably represents the upper rate of daily energy expenditure that can be maintained at a steady rate in heavy industry. Muller[3c] estimates that only about 4 per cent of the 25 million workers in Western Germany work to this degree and Passmore and Durnin[1] state that it is slightly higher than the rates recorded for British coal miners. At this rate of 5 Cal/min for 8 hours if 500 Cal is allowed for 8 hours in bed and 1400 Cal for the additional 8 hours off work, the total 24 hour energy expenditure is 4300 Cal.

For work which requires expenditure above the endurance limit increased rest pauses or increased absence from work occur. For such work Muller[3] makes the point that many small rest pauses relieve fatigue much more than a few long pauses.

An important area of knowledge of the cost of various activities is that involving individuals with physical disabilities or illnesses. Data are accumulating for those interested in intelligently regulating physical stress in chronic cardiac and pulmonary disease in convalescence and in correlating residual capacity with various demands of daily living in the orthopedically disabled. This subject has recently been reviewed by Gordon[5d] with tables of the cost of self care and occupational therapy activities. He emphasizes the energy costs of activities of the orthopedically disabled; for example, the requirements for ambulation by certain paraplegics for a period of only four minutes was comparable to that of a normal individual engaged in a 400 yard dash; unilateral above-knee amputees walking on level ground with a monoaxial knee joint required 25 per cent more energy expenditure than normal subjects at the same speed. The practical importance of such knowledge to the physician and other individuals who are concerned with aiding such patients is obvious.

It must be recognized that figures given in various tables of requirements, standards or allowances are merely approximations which are of value as guides in estimating needs of groups. The requirements of the individual worker may vary greatly from the average for his occupation. To the factors of size, age, sex and environment which affect calorie needs are added the variations in specific job situations and differences in activities between individuals on and off the job—all of which greatly influence the over-all calorie requirements.

Caloric deficiency resulting from inadequate food supply is one problem that the employed American has never had to face even in time of war. The so-called "food shortages" which have developed from time to time and which caused some difficulties in certain industries in World War II did not involve calorie insufficiency but rather an inability on the part of workers to get certain types of foods to which they felt they were entitled or which they believed they needed. For the majority of workers shortages of *calories* in the form of the more expensive animal products such as meat, milk, and eggs could be met easily by increasing consumption of cereals and other plant materials. Such a shift in dietary pattern, particularly if it were a pronounced one, would raise the problem of insuring an adequate intake of other nutrients and, equally important, that of maintaining

morale Even mild, involuntary changes in the food pattern in this country are not taken lightly Moreover, the possibility of nuclear warfare may thrust the problem of calorie deficiency of varying severity upon this country, as has happened in many other lands in earlier wars

The effects of such deficiency in man has been studied under conditions of actual food shortages, and in experimental situations, and a large literature exists which has been reviewed recently [7] In both acute starvation and semistarvation of some duration, physiologic, psychologic and some psychomotor changes are marked tests of intellective function show much less deterioration[7–10d] The degree of change in the various functions that occur depends upon the severity of the calorie deficit, its duration, and the individual concerned The effects of acute starvation are readily noted in endurance and personality changes within a few days [7–10d] The weakness and fatigue that develop are associated with reduction of voluntary physical activity to a minimum and with inability to carry out sustained hard work

With restriction of calorie intake in industrial situations, work output is curtailed accordingly A demand for heavy work output during a period of serious calorie deficiency would not be tolerated by workers for more than a few days and then only under emergency conditions An interesting example of the relation of productivity to food consumption was noted among German miners during World War II [11a] Young "cutters" in the coal mines had a daily output of 7 0 tons of coal per man on a total daily intake of 2800 calories, which was about 1200 calories above the estimated basal metabolic rate, or about 170 calories per ton of coal mined When 400 additional calories were allowed, output increased to 9 6 tons per man or 155 work calories per ton At this rate the men lost, on the average, 1 2 kg of body weight in six weeks The extra calories were raised to 800, whereupon the output increased to 10 tons per man and the body weight slowly returned to normal

It is well established that the body adapts to certain degrees of chronic calorie restriction In addition to a restriction of voluntary activity there is a decreased energy expenditure resulting from decreased basal metabolism and a decrease in the energy required to perform work, these savings are a result of the loss of body tissue [7,11b] The ability to preferentially metabolize body fat and to spare certain tissues, and to decrease the work of the heart further aids in withstanding lack of calories

The corollary question arises as to whether the composition of the low calorie diet has any influence on the organism's resistance to the deficit Only a relatively few experiments concerning this question have been performed with laboratory animals and still less with man, definitive answers are still lacking, particularly for long term situations It has been demonstrated in short term studies with rats[1] and dogs[13] that, when the caloric intake falls below 50 per cent of normal, dietary protein is used for energy purposes, in rats subsisting on low calorie diets a moderately high fat content (15 per cent) spares dietary protein to a much greater degree than low fat diets [1] In the case of young men, a diet supplying 950 calories daily did not prevent metabolism of dietary protein for energy purposes [14]

The Effects of the Frequency and Composition of Meals —Our custom of eating three meals a day probably is based more upon considerations of

convenience than upon those of physiologic need Experience in industry has shown the value to worker productivity of additional rest periods, particularly when associated with between-meal feedings The view is widely held that between meal snacks in themselves increase work performance and lessen fatigue This may be true, but there is no proof that frequent feedings increase physiologic capacity to perform work Undoubtedly, psychologic factors are important and account for some, if not all, of the beneficial results observed

Haggard and Greenberg[15] found that high carbohydrate intake increased muscular efficiency in laboratory exercises on the bicycle ergometer and that variations in efficiency were correlated with the length of time between meals They then carried on experiments with employees in a shoe factory in which productivity was measured during periods when 3 or 5 meals per day were eaten, and concluded that 5 meals a day resulted in superior work performance (about 40 per cent increase in productivity) *Unfortunately, the laboratory findings of these investigators do not agree* with data obtained by other workers and the reported changes in muscular efficiency have not been confirmed [16–18] The study with shoe operators was not sufficiently well controlled to entirely rule out psychologic effects, as Ivy[19] has pointed out These criticisms of course do not dispose of the finding that there was increased production with an increase in the number of meals There have been similar reports [0–] of improved efficiency or well being with increased meals but the 'morale factors have never been ruled out

Haldi and Wynn [3] studied the productivity of seamstresses as influenced by different amounts and kinds of food consumed during the mid-morning and mid afternoon rest periods No differences were noted in work output when the caloric intake was varied from 80 to 650 calories and the type of food from a soft drink to a small meal Less definite evidence indicated that omitting all food during the rest period did not decrease production this particular aspect of the problem could not be thoroughly assessed because the *women objected to being denied the opportunity to partake of* food during the rest period In the Hawthorn experiment [24] when women engaged in assembling telephones were given extra snacks their output increased however, when they were given a rest period without food, their output also increased Many other changes in working conditions increased output and it became apparent that a very important general factor influencing productivity was the knowledge on the part of the worker that management was concerned about her welfare and views In a recent review Hutchinson [5] discusses the problem of meal habits and the frequency of meals and advocates a regimen of 6 meals daily However, no convincing nutritional or physiologic evidence is given to support this proposal for the usual industrial situation Pyke who has had considerable experience with industrial feeding in Great Britain has summarized his experience and views on the subject of feeding *individuals doing moderate* work by concluding [6]

'(a) Provided the daily diet supplies the full needs for nutrients the number of meals into which it is divided does not appear to be crucial

"(b) The nutritionist must always remember that industrial efficiency is influenced by very many factors other than diet

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convenience than upon those of physiologic need. Experience in industry has shown the value to worker productivity of additional rest periods, particularly when associated with between-meal feedings. The view is widely held that between-meal snacks in themselves increase work performance and lessen fatigue. This may be true, but there is no proof that frequent feedings increase physiologic capacity to perform work. Undoubtedly, psychologic factors are important and account for some, if not all, of the beneficial results observed.

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"(a) Provided the daily diet supplies the full needs for nutrients, the number of meals into which it is divided does not appear to be crucial.

"(b) The nutritionist must always remember that industrial efficiency is influenced by very many factors other than diet."

Until more definitive experimental work demonstrates the contrary, we concur with this view.

Since an appreciable number of workers are believed to report for work without having eaten any breakfast or only a cup of coffee and toast or sweet bun, it is of some interest to note reports on attempts to assess the results of different types of breakfast and of no breakfast on test subjects. Tuttle and co-workers[7–29] found that maximum work output attainable on the bicycle ergometer within one minute, muscle tremor, and choice reaction time were adversely affected on omission of breakfast or by the consumption of only black unsweetened coffee, as compared with performance with breakfasts supplying from 300 to 1000 calories. The differences appear clear-cut for the majority of subjects tested. While some individuals apparently were not affected by omission of breakfast, others reported dizziness, nausea and vomiting during the period of omission of breakfast. Whatever the nature of the physiologic and/or psychologic basis of the results, the results would appear to warrant consideration of the practical applications.

A study of the short-term (two-day) effect of a "breakfast" consisting only of unsweetened black coffee showed the expected absence of a rise in blood sugar above the fasting level and a slight decline throughout the subsequent three-hour period.[30] Unfavorable subjective symptoms were often reported in the morning, including hunger, weakness, headache, and lassitude. When this type of breakfast was followed by a lunch consisting of a low-protein, low calorie sandwich and coffee, a transitory high blood sugar developed which dropped by the third hour to levels below those found during fasting. This fall in blood sugar was accompanied by subjective symptoms of hypoglycemia. An intake of 300 calories at breakfast decreased the blood sugar drop after the low protein luncheon, and increasing amounts of protein and fat were associated with improved sense of well-being and flatter blood sugar curves. A similar type of experiment conducted over a period of weeks or months would be worthwhile in order to learn whether adaptation to omission of breakfast occurs. A study of the effect of omission of lunch and of three types of lunch (standard, high fat and high carbohydrate) on the ability of men to perform strenuous work revealed that the intake of meals affects performance and fatigue of visual functions.[31] No single type of meal (including no food at all) was superior or inferior for all of the functions measured in the fairly large battery of tests which were applied. However, it was concluded that, in general, the standard meal (carbohydrate 50 per cent, protein 12 per cent and fat 38 per cent of the 1300 calories) and the high fat meal (fat supplying 83 per cent of the 1400 calories) were preferable for this type of work.

It would appear, then, that omission of breakfast is likely to decrease work efficiency, if only through a feeling of discomfort. A poor lunch, in addition, strengthens this possibility and places the burden of providing the major share of nutrients on the evening meal.

Despite the fact that Liebig's theory that protein is the fuel of muscular work was disproved in 1866, the suggestion is still occasionally made that persons doing hard work need increased proteins. Chittenden[3] in 1904 reported that men performed hard work and increased in vigor on a daily

high carbohydrate diets nor did they find that a high carbohydrate breakfast before exercise caused a hypoglycemic reaction [17,18,39]

Thus, it would appear that inclusion of breakfast in the eating pattern is of some benefit in reducing mid-morning discomfort While the source of calories is not critical and we cannot assess the value of protein in terms of industrial efficiency, an intake of 15 or more gm of protein slows the blood sugar fall and may be associated with a sense of well-being lacking in low protein breakfasts Information is lacking on the optimum meal composition for specialized types of work, however, on the basis of available data it is not likely that any particular formula will be optimum for all of the complex functions involved in the physiologic activities of industrial work

Vitamins —The signs and symptoms of various vitamin deficiencies, the beneficial effects of therapy, and human requirements have been discussed in detail elsewhere in this volume (see Chapter 11) It suffices to mention briefly in this chapter the relation of vitamin intake to physical and mental efficiency and to resistance to various physiologic stresses which may occur in industry

It must be borne in mind in considering the information given below that, although practically all experimental work on the relation of nutrition to fatigue employs physical stress to produce fatigue, most modern industrial work fails to tax the physical endurance of the average worker The type of fatigue of greatest importance to industry is that involving the central nervous system a type that has been the subject of relatively little scientific study

The evidence leaves little room for doubt that the earliest symptoms of human deficiencies of those water soluble vitamins about which we know most are those of easy fatigability, anorexia irritability, and apathy The ability to perform work efficiently is impaired in frank deficiency states and adequate therapy will restore work capacity toward normal levels as will the adequate treatment of other types of illness where permanent incapacity is not involved

Vitamin Supplementation of Presumably Adequate Diets —Simonson and co-workers[43] found no effect on 5 different types of muscular work with the addition of large amounts of the vitamin B complex to the usual diet of 12 healthy subjects The vitamin B surplus did however, increase the fusion frequency of flicker (possibly a measure of central nervous system fatigue) in 8 of the 12 subjects, and all 12 subjects experienced subjective improvement of working capacity

The experiments of Keys and his group indicate no beneficial effect of supplementation with 5 B complex vitamins and ascorbic acid on muscular ability, resistance to fatigue or recovery from exertion of healthy young men subsisting on diets considered to be adequate [44a] In experiments lasting ten to twelve weeks and utilizing normal young men, it was found that intakes of thiamine at 4 different levels (from 0 23 mg per 1000 calories daily up to 0 63 mg per 1000 calories) exerted no beneficial effect on diets otherwise considered adequate Muscular, neuromuscular, cardiovascular psychomotor, and metabolic functions tested "were in no way limited—(and) clinical signs, subjective sensations and state of mind, and behavior

were likewise unaffected "[44b] A level of 0 96 mg of thiamine per 1000 calories was allowed to the control subjects in these experiments Supplementation with B complex vitamins of a diet considered adequate did not increase the endurance of several subjects operating a bicycle ergometer[46]

A more recent experiment with 86 volunteer military personnel exposed to a cold environment revealed no significant difference in physical and psychological performance in a ten week test between supplemented and unsupplemented groups[45] The supplementation consisted of large amounts of 7 B complex vitamins and ascorbic acid The basal diets were presumed to be adequate except for a 3 week period of moderate caloric deficit

The addition of 75 mg of ascorbic acid to diets already adequately provided with this vitamin has been found to exert no detectable effects in terms of general well being, physical vigor, and efficiency for hard work[47] Performance in 3 athletic tests was studied in 2 large groups of South African native miners subsisting on the usual compound diet One group was given a daily supplement of orange juice containing 40 mg of vitamin C and the tests were repeated at intervals over seven months No differences were observed in ability to sprint 100 yards, run a mile, or put the shot[48]

During 1941 to 1943 a combined study of dietary habits, clinical status, and the effect of nutrient supplementation was conducted by Borsook and his associates on large numbers of aircraft workers in Southern California[49–53] No significant specific therapeutic effects of a multiple vitamin-mineral supplement (vitamins A, D C, B_1 riboflavin niacinamide, and calcium) were observed However, the supplemented group was reported[51] to show decreases in unauthorized absences and turnover rate as compared with the group receiving a placebo

This evidence supports the general opinion that once the vitamin requirements of the organism are met there is no value in additional supply *i e* "super nutrition ' does not exist

Effects of Low Nutrient Intake on Efficiency —Consideration of this topic involves one in a highly complex subject characterized by conflicting evidence and opinion Johnson *et al*[54] found that young men subjected to hard daily physical work and subsisting on a diet deficient in members of the B complex, notably thiamine exhibited symptoms of easy fatigability, apathy, muscle and joint pains, anorexia and constipation and a marked deterioration in work performance within one week Another group on the same diet supplemented with thiamine exhibited only a few mild subjective symptoms, but their performance during hard work also deteriorated Administration of yeast restored both groups to normal within four days

Foltz, Barborka, and Ivy[55] studied the work performance on the bicycle ergometer of 4 medical students When the thiamine intake was reduced from 0 43 to 0 59 mg per 1000 calories of food to 0 33 to 0 38 mg per 1000 calories a decrease in appetite was noted within three weeks After one month at this reduced thiamine intake a further decrease in thiamine intake was effected (0 17 to 0 21 mg per 1000 calories) but no additional changes were noted until four weeks later, at which time a decided decrease in appetite and work output occurred, together with increased fatigue and

muscle tenderness and a deterioration in mental attitude. The objective and subjective symptoms disappeared promptly after the addition of a yeast concentrate. Archdeacon and Murlin[56] noted a decrease in muscular endurance on the bicycle ergometer in 2 subjects on a diet low in the B complex vitamins (the thiamine intake being 0.27 mg. per day or 0.09 mg. per 1000 calories), the effect being observed within ten to fourteen days on the diet. Addition of the B complex in the form of whole wheat bread or thiamine in pure form resulted in a marked improvement in endurance. Pyridoxine added in one experiment had a similar effect but riboflavin had none.

These results are in marked contrast to those of Keys and co-workers. In one experiment[44] already mentioned, no decrease in work performance was noted on diets containing 0.23 mg. thiamine per 1000 calories. In a later paper[57] the Minnesota investigators published the results of a study in which 8 young men were studied before, during, and after a two-week period during which 5 were on a basal diet providing on the average 0.16 mg. of thiamine, 0.15 mg. of riboflavin, and 1.8 mg. of niacin per 1000 calories. These men also received placebos while 3 control subjects were given the same basal diet plus capsules containing a yeast concentrate and synthetic B vitamins. With an energy expenditure of 4800 calories during the experimental period, no differences were noted in endurance and in a variety of clinical, psychologic, and biochemical tests.

In more recent experiments[58] the length of time on a low B complex intake (0.185 mg. thiamine, 0.287 mg. riboflavin, and 3.71 mg. niacin daily per 1000 calories) was extended to one hundred and sixty-one days and again no impairment of work performance was noted at a calorie intake and expenditure of 3300 calories. A small increase in blood pyruvate indicated a borderline thiamine deficiency. Immediately thereafter the intake of 2 of the subjects (known as the restricted-deficient group) was restricted much more severely to 0.008 mg. thiamine, 0.013 mg. riboflavin, and 0.1 mg. niacin daily per 1000 calories with a daily energy intake and expenditure of 4000 calories. Anorexia developed after the first week and by the end of the third week the subjects exhibited almost complete inability to take any food. Supplementation was begun with thiamine alone on the twenty-fourth day. Two additional men who had been on an adequate diet prior to ingesting the very deficient diet (the control-deficient group) exhibited anorexia to a lesser extent. Despite marked changes in general behavior and obvious signs of subjective distress, there were no significant changes in simple strength as measured by grip and back lift. Psychomotor tests of speed and coordination showed slight to marked deterioration. The restricted-deficient subjects showed a rapid and progressive deterioration and incapacity to perform brief severe work. Nausea developed on extreme exertion. Similarly this group was often unable to complete the prescribed daily exercise of moderately hard work, while the control-deficient group was able to perform both types of work. The administration of thiamine alone reversed the deterioration.

It is worth noting at this point that even severe thiamine deficiency does not cause any significant diminution in ability to perform intellectual

tasks, although marked deterioration takes place in certain psychomotor and personality tests and endurance[59a 59b 10a]

Another experiment[60] bearing on this problem involved the maintenance of 7 young men for thirty-five weeks on a diet that was low in vitamin B complex at a calorie level of approximately 3000 After five weeks, 2 of the subjects received supplements and acted as controls In the subsequent period the latter showed no decrease in work performance or physical or psychologic appraisal, while the 5 experimental subjects showed definite deterioration in work performance after fifteen weeks on a daily intake of 0 50 mg thiamine, 0 30 mg riboflavin, 5 8 mg niacin low levels of the other B vitamins and 45 gm of protein (94 per cent from non-animal sources) When the diet was supplemented with crystalline vitamins, improvement in physical performance tests occurred gradually No evidence was obtained pointing to an outstanding effect of any one nutrient and improvement was more rapid in subjects receiving the complete group supplementation than in those receiving step-wise additions of nutrients

One can only conjecture about the reasons for the discrepancy in results obtained in different laboratories with intakes of thiamine in the same range There were obvious differences in the subjects diets and experimental conditions It cannot be overemphasized that in the study of the effects of nutritional deficiencies upon functions of the human subject, careful consideration must be given to both psychologic and physiologic factors which may influence the results Since subjective reactions and individual variability are serious complicating factors in such experiments one must exert the greatest caution in accepting the conclusions of experiments not rigidly controlled

In the only report published on the effects of uncomplicated low riboflavin intake on muscular performance the Minnesota group[61] found no deleterious effects in 3 men after eighty four days and on another 3 men after one hundred and fifty-two days on a diet containing 0 99 mg riboflavin per day This level of riboflavin will not cause the development of obvious clinical signs even over a period of two years in less active individuals[6]

In a study[63] of experimental human ascorbic acid deficiency induced by a diet very low in the vitamin, the first symptom was fatigue which appeared after two months An impaired capacity for walking and running progressed during the six month deficiency period A similar effect of vitamin C deficiency was noted by Farmer[64] in experiments with a group of young men existing for several months on a diet low in vitamin C

In view of the ability of the body to store sufficient vitamin A so that deficiency signs may not occur for a year or more on an A-vitamin deficient diet,[65] it is not surprising that no decrease in ability to perform hard muscular exercise was noted in men kept on diets low in vitamin A for about six months[66]

Do vitamin requirements increase as energy expenditure rises? In this connection Forbes[67] has pointed out three possibilities, namely The requirements may be either (*a*) practically unaltered, or (*b*) increased in proportion to the work or (*c*) increased in proportion to the displacement of the equilibria of the body that is show little change until the work

becomes really hard and then show a great increase." There is a fourth possibility, namely, a relatively large requirement for basal metabolic purposes, with smaller increases associated with increased work and increased calorie intake. From indirect data on human dietaries associated with the presence or absence of beriberi, and on the basis of animal experiments where the amount of activity or the environmental temperature were varied, or where experimental hyperthyroidism was induced, it has been concluded generally that the requirement for certain B complex vitamins, particularly thiamine, is related to total metabolism. In the 1945 Revision of the Recommended Dietary Allowances of the Food and Nutrition Board of the National Research Council[68] it is stated:

"In the original table the thiamine allowances for the several categories were based on the concept that a definite ratio exists between calories and thiamine throughout the entire caloric range. In the conference of consultants in preparation for the 1945 revision it was agreed that the proportion of thiamine required decreases as the calories increase above the lower levels."

In the 1948, 1953 and 1958 revisions of the Recommended Dietary Allowances[69] the practice is retained of recommending increased thiamine and niacin intake for increased caloric expenditure. The explanation in the 1948 revision that "the fact that figures are given for different calorie levels for thiamine and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation" would appear to continue to be true at this time.

In the 1945 revisions the Food and Nutrition Board adopted the procedure of maintaining approximately the ratio 3:2 between riboflavin and thiamine requirements and 10:1 between niacin and thiamine. However, in the more recent revisions, riboflavin allowances are based on body weight rather than calorie level. Since there is a similar relation of protein to body weight, the riboflavin allowances are computed from the protein allowances, using a factor of 0.025.

The 1948 Canadian nutrition standards continue to suggest a very close relation between calorie expenditure and requirements for thiamine, riboflavin, and niacin.[70] The author believes that the available experimental evidence provides scant evidence for a close relation between calorie need and riboflavin and niacin requirements.

Although work ability is markedly diminished in severe vitamin C deficiency states,[63,64] it is doubtful that hard work brings on scurvy more rapidly. Experiments in which both sedentary and working men were kept on scorbutic diets for eight weeks failed to show any difference between the groups.[48] Fox,[72] in a review of European and South African literature on the effect of exercise on vitamin C metabolism and needs states that the evidence is inconclusive. This same investigator analyzed the histories of over 1000 cases of scurvy occurring in a five-year period among South African native miners and concluded that there was no evidence to suggest that those engaged in strenuous work developed scurvy more often or more quickly than those whose metabolic resources were taxed less severely.[73]

While the evidence is still far from satisfactory on this subject it appears

that no radical elevation in requirements for the vitamins is associated with increased physical activity However, as noted above, some increase in thiamine with lesser increases for niacin is desirable with increased caloric expenditures

NUTRITIONAL AND ENVIRONMENTAL STRESS

Influence of Cold Environment on Nutrient Requirements —It is generally held that caloric requirement increases as environmental temperature falls Johnson and Kark [4a] in their studies of soldiers voluntary caloric intakes in different areas from the tropic to arctic were led to postulate a linear function in the increase of calories with decreasing temperature Average daily intake varied from 4400 Cal per man in the cold to 3200 Cal in the tropics with the proximate composition of the diets selected being much the same in all climates The authors stated their belief that expenditures for a given task were greater in the cold than in warm climates because of the hobbling effect of arctic clothing and equipment and because of the need for more heat to maintain thermal equilibrium

The Food and Agriculture Organization of the United Nations[6a 6b] and the Food and Nutrition Board of the National Research Council[68] have accepted this inverse relation and recommending increases in caloric allowances for each 10° temperature decrease

This viewpoint has been questioned on the basis of food consumption data by Alaskan troops and Eskimos,[74b] by troops in northern Canada,[74] and by a comparative study[74d] of troops, carrying out similar tasks in Fort Churchill, Canada (mean temperatures −22 5° F and −7 3° F at 2 different periods), Massachusetts and Yuma, Arizona (mean temperatures 72° F and 91° F, respectively) These reports agree on the point that caloric consumption in the cold climates was not dissimilar to that in temperate areas, especially when calculated on an equal weight basis The latter study included measurement of the energy expenditure by men in the three environments at sedentary activities and that necessary to walk at 3 41 miles per hour The values were found to be similar on a body weight basis

The efficiency of arctic protective clothing and the present ability to heat base camps have reduced markedly the problem of maintaining body warmth at the expense of additional muscular activity or outright shivering It would appear that the ambient temperature is often not a major influence on increasing caloric requirements, but rather the hobbling effect of arctic clothing and equipment, as originally pointed out by Kark and Johnson [4a]

Le Blanc's data[74c] suggest that under arctic and subarctic living conditions many individuals are likely to consume excessive amounts of food due to isolation boredom and other abnormal living conditions

Studies with human subjects show that diet and the frequency of feedings may have an effect upon the ability of man to withstand exposure to intense cold [75 76] The cooling of the internal tissues of the body was found to be most rapid on a high protein diet (41 per cent of calories as protein) and least on a high-fat diet (73 per cent of calories) with a high-carbohydrate diet (66 per cent of calories) not quite so effective as a high-fat

diet The least favorable method of feeding tested was the high protein diet with 1 meal (20 per cent of the day's calories) served during an eight hour exposure, and the most favorable method was the high fat diet with 3 meals (20 per cent) served during eight hours of exposure By a change from the first to the second diet plan, the decrement in rectal temperature was reduced by two thirds (1 63° to 0 57 ° C) and the decrement in general psychomotor functioning by one-half [76]

With the increased calorie expenditure occurring in cold climates, it is probable that vitamin requirements are not markedly altered from those in temperate climates, there may be small increases for some of the B vitamins as a result of increased calorie expenditure Troops in an Arctic environment subsisting on a diet meeting the Recommended Allowances of the National Research Council did not appear to be noticeably benefited by vitamin supplements [77] A short term (three month) study of performance of young men under cold stress during "borderline" and high intakes of thiamine and ascorbic acid did not reveal any significant differences attributable to these vitamins [78] In conformity with the animal experiments of Dugal *et al*,[79a] a decreased ascorbic acid excretion was noted in the urines of these men during cold stress

Experiments with animals exposed to cold have been reported by Dugal and colleagues[79b] in which the influence of diet on survival and growth were noted In these respects a diet rich in fat proved much better for rats kept in a cold room than an equicaloric diet high in carbohydrate

More recent animal experiments[79c] support the view that increased amounts of fat allow better maintenance of body temperature and survival in the cold However, Sellers *et al*[79d] found that no consistent difference in rate of survival or increase in body weight occurred in rats living at 1 5° C and subsisting on various diets with a constant content of protein and containing 5 to 44 per cent of fat

Interestingly, animals exposed to cold utilized relatively low amounts of protein more efficiently and deposited less fat in their livers on a high fat intake than did those in a comfortable environment [79e]

In experiments conducted upon the guinea pig, which, like man, requires an external source of vitamin C, it was found that adaptation to cold (as measured by weight gain) depended on the intake of ascorbic acid [79a]

Similar studies on the nutritional requirements for resistance by the rat to cold stress have indicated that there is significant impairment in deficiencies of thiamine,[80] riboflavin,[81] pyridoxine [8] vitamin A[83] and pantothenic acid [84] A contributing, but not the sole, factor in the decreased survival to cold is the impaired caloric intake by the deficient rats [84]

In summary, it would appear that, on the basis of our present knowledge, the chief effect of cold on dietary requirements is the increased need for calories Where clothing is insufficient to keep the individual warm, body temperature may be better maintained by more frequent meals containing a greater than usual percentage of fat There appears to be no significant increase in need for vitamins beyond that associated with increased calorie expenditure

Requirements in Hot Environments —The altered nutritional requirements during exposure to heat are quantitative rather than qualitative and

involve mainly water and sodium chloride. As the environmental temperature rises in relation to the body temperature the flow of heat from the body to the environment is impeded. In an attempt to maintain its usual temperature, the body secretes sweat, the evaporation of which removes heat. Water and sodium chloride are the only components of sweat which are apt to be lost in amounts large enough or rapid enough to lead to a condition of deficiency. The amounts of other elements lost in this way are not significant.[71,85] The claim that sweat is an important avenue for loss of body iron[86] has not been supported by the work of others.[87,88]

The capabilities of the body for sweat loss are great; for example, in one experiment in which young men were subjected to severe stress of temperature and work,[89] the maximum sweating rate was 4.2 L. per hour and some men completed four hours of work while sweating at rates of 3 L. per hour, a total amount equal to approximately 4 times the blood water. While this high rate is not met in industry except in exceptional short-term situations, the loss of 1 L. of water per hour for an eight hour day occurs at times in certain heavy industries and with this volume of water, a total of perhaps 10 to 20 gm. of salt. Dill *et al.*[90] noted a maximum daily water intake of 11.4 L. among some steel mill workers.

No ill effects occur through such large losses, if the water and salt are replaced periodically. However, if proper replacement of salt and water is not made, undesirable consequences occur, ranging from decreased physical and mental performance to death.

A number of investigators have demonstrated that, in a matter of a few hours, the physical status and performance of subjects in a hot environment and doing hard work deteriorate (proceeding under severe conditions to actual collapse) when water is withheld.[91–96] Administration of water under these circumstances enables the body to maintain lower rectal and skin temperatures, more normal pulse rates, and mental efficiency. Symptoms of acute water lack during hard work in a hot environment appear to be the most rapidly induced of any deficiency syndrome. Recovery from the effects of dehydration following water ingestion is even more rapid.

Thirst is a reliable guide to water needs under most circumstances. However, men sweating even at moderate rates do not tend to drink water as fast as they evaporate it, although they usually make up the deficiency after the day's work.[97] When the heat load is very high and continued, thirst may fail to insure an adequate intake.[8,96,98] It has been recommended[85,99] that men working in the heat replace the water lost in sweat by hour-to-hour ingestion of amounts more than sufficient to keep thirst quenched at all times. In hot environments with hard work and given optimal osmotic balance a minimum of 2.8 liters per day is required to prevent cessation of sweating and ultimate heat stroke.[99a] For light work work in hot environments a minimum of 1.9 liters per day is required to prevent anhydrosis.

The effects of salt deficiency among industrial workers were first pointed out by Moss[100] in connection with "miners' cramps." Since then it has been noted in a variety of occupations among workers exposed to elevated temperatures. The basis of this deficiency is failure to replace adequately the sodium chloride lost in sweat, while the water loss is made good. Symp-

toms may include nausea, vomiting, vertigo, mental apathy, exhaustion, painful cramps, and circulatory failure. It is important to note that heat exhaustion due to salt deficiency is not always associated with heat cramps.[101,102] Workers in hot environments should have ready access to water (preferably cool but not cold) at all times and they should be instructed as to the importance of frequent water and adequate salt intake. Since the average American's daily diet contains 10 to 15 gm. of salt and as salt lost in sweat need not be replaced hourly, the salt consumed at mealtimes is adequate for most needs. It is desirable, however, for workers consuming more than 4 quarts of water daily to supplement their dietary salt intake by 1 gm. of salt for each additional quart of water consumed. This is most satisfactorily supplied in the drinking water in concentrations not higher than 0.2 per cent.[85,99,103] The use of salt tablets is less desirable since they frequently cause gastric distress, nausea, and vomiting in some individuals, especially during hard work and, more importantly, there is no assurance that those needing salt most will take the tablets. Under circumstances where salted drinking water is not feasible, a slower dissolving cellulose-impregnated salt tablet[104] may be more desirable than the usual salt-cornstarch tablet.

Both from theoretical considerations and from actual experience, protein foods are as suitable in hot as in cool climates. Recent work has indicated that the specific dynamic action of protein *in mixed diets* is less than the specific dynamic action of protein when fed alone.[105,106] However, even on the basis of the usual figures for the specific dynamic effect of protein, Johnson[85] has calculated that a meal rich in protein would strain the heat dissipating mechanisms at the most only 5 per cent as much as moderately hard work (march at a standard Army pace). He concludes that "Although theoretically, at some critical temperature this extra 5 per cent might be a factor limiting work, practically, a high protein diet has little if any deleterious effect upon efficiency for work in the heat." Johnson and his co-workers[107] found that varying the daily protein intake in successive two-month periods from about 100 to 150 to 75 gm. and back to 100 gm. had no deleterious effect upon ability to march on a treadmill for relatively short periods in humid heat or to perform very hard work of short duration in a temperate environment. These workers challenge the recommendation of Lusk[108] that a high protein diet is contraindicated in hard work especially in hot weather. Certainly, the fact is well established that acclimatized men in tropical areas who have access to meat eat it and often in large amounts, without obvious untoward reactions.

Amino acids are lost in sweat, however, with a sweat volume of 3 L. per day, the loss of essential amino acids is not likely to exceed 1.5 gm.[109] With a greater and long continued sweat volume, amino acid loss may be significant, particularly if proteins of poor biological quality are consumed and if adaptation to climate does not reduce the loss. Information on the latter question is lacking.

Although there are no well-established figures for optimal intakes of fat or carbohydrates and one cannot speak of actual requirements for these nutrients, it appears that the usual pattern of dietary intake need not be altered in hot climates in order to perform work. It is of interest to note

that Forbes *et al* [105] found that, in rats, the specific dynamic effect of a mixture of fat and protein is somewhat less than half that anticipated from the values of the individual nutrients, and that the addition of fat to carbohydrate or protein or a mixture of the two lowered their dynamic effects If these findings apply to man, then fat in the diet in hot climates should tend to lower heat production

At least two possibilities exist for changes in vitamin requirements of men at elevated temperature losses in sweat and altered metabolic requirements Losses of vitamins in sweat were studied in a number of laboratories during World War II [71] The evidence supports the conclusion that in absolute amounts and in comparison with the urinary excretion of the water-soluble vitamins, losses in sweat are not a significant factor in depleting the body s stores There is no evidence that metabolic requirements are increased On the contrary, the observed increased urinary excretion of pantothenic acid and ascorbic acid may possibly mean a lowered requirement at elevated temperatures Some popularization of the belief that the need for ascorbic acid is increased has resulted from reports[110 111] of benefits from large amounts of vitamin C given to workers and from reports[11] that, in hyperpyrexia of infective or artificially induced origin, plasma ascorbic acid levels are reduced However Osborne and Farmer[113] were unable to find any reduction in plasma ascorbic acid in patients exposed to a temperature of 102° F in fever cabinets, and Abt and co workers[114] concluded from studies on infectious diseases that hyperpyrexia alone did not affect the vitamin C reserves or utilization No beneficial effect of large amounts of vitamin C was noted on the ability of young men to work in hot environments for short periods (three hours to four days) nor were there any apparent effects on temperature, vasomotor stability, psychomotor, or strength responses, or on resistance to heat exhaustion [115]

This subject gained new interest as a result of a series of papers by Mills and co-workers[116 117] in which the claim was made that in a hot (91° F) moist environment the requirements for growth of rats for certain vitamins, specifically thiamine and choline were increased over those at 75° F while the requirements for riboflavin and other vitamins were not affected It should be noted that in this work the vitamins were incorporated in the diet so that their intake varied directly with the quantity of the diet ingested When thiamine in different amounts was administered to rats separately from the ration, it was found that an increase in environmental temperature resulted in a *decreased* thiamine requirement [118 119] These authors believe that this decrease approximates the decrease in calorie requirement at the elevated temperature

Mills has admitted[1 0] that the absolute thiamine requirement in micrograms per rat per day may be largely unaffected by temperature However, he makes the point which is important in itself, that vitamins are usually ingested as part of the diet, and whenever food intake decreases as a result of high temperatures, a diet adequate in temperate climates may become inadequate with respect to one or more nutrients Anorexia and finicky appetites in men exposed to high temperatures are not uncommon and this point is well taken However it should not be construed as prov-

ing an increased metabolic requirement It suggests, rather, that the diets of workers at high temperatures, who find difficulty in eating properly, should be given careful attention

Anoxia and Low Pressure —Although it was suggested in 1908[121] that a carbohydrate diet would be beneficial in alleviating systems of oxygen lack at high altitudes, detailed investigations on human subjects awaited World War II with its emphasis on aviation Good biochemical and physiologic data, on men and experimental animals, support the belief that diet affects human altitude tolerance

King and co-workers[12, 123] have carried out studies on the effects of different diets in human subjects maintained at the equivalent of 15,000 to 17,000 feet with oxygen, on whom corticoretinal (peripheral vision) and psychomotor function tests were performed and whose pulse and respiration rates as well as performance ratings were noted Significant gains in altitude tolerance for periods up to six hours could be accomplished by the ingestion of preflight and inflight foods of high carbohydrate content, in contrast with performance after the omission of a meal, after a single meal high in protein, or after large amounts of fat These authors emphasize that their findings pertain to immediate preflight and inflight meals which then can be followed by meals correspondingly high in protein, so that there is no departure from normal requirements or accepted dietary practices relative to food intake as a whole Other studies employing human subjects have generally supported these findings[124, 125]

There is no evidence that mild vitamin deficiency states have any effect on human altitude tolerance[126]

Aero embolism or decompression sickness has been a problem encountered by flyers at high altitudes in non-pressurized planes While diet is not likely to be a very significant factor influencing this condition, it is worth mentioning that experiments employing a relatively small number of subjects suggest that high carbohydrate diets decreased aero-embolism as compared to high fat or high protein diets[127]

Under conditions of lowered pressure, gases in the gastrointestinal tract will expand and will, under certain conditions, cause abdominal pain which may become very severe The drinking of carbonated water and the consumption of melons prior to flight would appear contraindicated[128] While the ordinary variations in the proportions of protein, fat, and carbohydrate in the diet did not appear to be associated with susceptibility to abdominal gas, a diet containing about 20 per cent of the calories as protein and 53 per cent as fat proved superior to high carbohydrate or normal diets in decreasing the incidence of abdominal pain and its severity The importance of the kinds of foods consumed prior to flight on abdominal gas has been reported also by Tillisch[129] Meals containing fried meat, beans, cabbage, green leafy vegetables and raw fruit when eaten a few hours before ascent caused many more cases of severe abdominal gas pain than bland meals consisting of roast beef without gravy, mashed and puried vegetables and stewed fruit

For further information on nutritional relations to heat, cold, and anoxic stress reference is made to the recent book of Mitchell and Edman[11]

NUTRITION AND SUSCEPTIBILITY TO TOXIC COMPOUNDS

Although emphasis in the prevention of industrial poisoning must rest on elimination of hazardous situations, nevertheless circumstances still do arise in which technological measures fail to keep dangerous chemicals within safe limits It is of interest then to know whether nutrition can exert either a protective or therapeutic action against certain poisons

If significant effects can be demonstrated, then they may have practical value in industrial and clinical medicine In addition such a relation may also help explain the puzzling phenomenon of individual variation in susceptibility to toxic substances Two broad questions which present themselves are Can nutritional factors influence resistance to toxic substances? and, Are nutritional requirements of the individual altered by exposure to poisons?

Unequivocal evidence on the first question from studies in industry simply does not exist The centuries old custom of giving milk to workers exposed to lead has never been proved to have a specific protective value Aub and co-workers[130] and Kehoe *et al* [131] for example were unable to find any significant influence of milk upon lead absorption from the gastro intestinal tract

One of the early modern attempts to influence susceptibility by dietary means was the dietary reform program inaugurated in 1917 among female employees exposed to TNT in an English ordnance plant [13] A marked success was attributed to this program with the claim that the incidence of gastro intestinal disorders fell from about 12 per cent to less than 2 per cent This report has been quoted rather widely as evidence for the beneficial effect of diet in increasing workers resistance to TNT However a reading of the original paper reveals that there was no control group employed, and that the sickness rate ascribable to TNT poisoning varied tremendously from month to month and over a period of months Under such conditions the claim for a dietary effect has no firm support

Since that time a number of statements have been made recommending dietary measures for prophylaxis or therapy in munitions and chemical industries These recommendations have included the use of high carbohydrate and low-fat diets large amounts of ascorbic acid, calcium, milk, multiple vitamin formulas, and a combination of various other nutrients Uniformly, these suggestions have failed to be accompanied by convincing evidence to support them

We are therefore forced to turn to the results of animal experiments for light on this problem and here we find overwhelming evidence that nutritional state has a profound effect on the relative toxicities of a very large number of substances of both inorganic and organic nature Among these substances are included many that are used in industry such as benzene, chlorinated hydrocarbons, aromatic nitrobenzene derivatives, glycols and others Susceptibility to x irradiation and radioactive materials can also be altered by dietary means

An experiment which undoubtedly will rank as a classic in this field is the work of Miller and Whipple[133] who studied the effects of chloroform

anesthesia in dogs in which the body protein had been depleted by diet or plasmapheresis. It was observed that these dogs were extremely susceptible to liver injury by chloroform; thus, exposure of fifteen to twenty minutes' duration caused fatal hepatic damage in protein-depleted dogs, while sixty minutes of anesthesia was well tolerated with little or no hepatic damage by dogs receiving a diet containing ample protein. It was further shown[134] that the sulfur-containing amino acids DL-methionine and L-cystine, when given before chloroform anesthesia, were equivalent to the feeding of whole protein in preventing fatal hepatic injury. A variety of other amino acids failed completely to protect protein-depleted dogs.

Many other experiments have been reported from a number of laboratories emphasizing the deleterious effect of a low protein intake in animals receiving a variety of toxic substances.[135–137] The use of the terms "low protein" diet or "high protein" diet merits some comment at this point since they are not always correctly employed by workers in this field. The terms, in order to be nutritionally meaningful, should bear a relation to the level of protein required by the particular species tested and to the age of the particular animals used in the experiment. Thus, an actively growing rat requires about 20 per cent of the protein casein in the diet for optimum growth, while a fully grown rat requires much less to maintain weight and health; an adult dog can maintain weight and nitrogen balance with about 8 per cent protein, but a growing dog needs more. A "low protein" diet, then, should be one containing protein at some level below minimum requirements for normal growth or maintenance, while a "high protein" diet should have the protein well above the minimally adequate level.

It is well known that a diet inadequate in protein results in a deficiency, among others, of methionine, an essential amino acid which acts as a source of labile methyl groups. Deficiency of labile methyl groups results in fatty liver. Goldschmidt, Vars, and Ravdin[138] were among the first to note, in their studies on the effect of diet on chloroform susceptibility, that the incidence and severity of damage to the liver in dogs increased progressively with the content of fat in the liver and was independent of the initial content of hepatic glycogen. Many studies with chlorinated hydrocarbons have revealed that high fat diets are more toxic than low-fat diets. High-fat diets associated with a low content of protein and lipotropic substances, such as choline, result in fat accumulation in the liver. For some reason a fatty liver is more easily damaged than one with normal fat content and fatty liver cells do not seem to regenerate as quickly as normal cells.[139] Thus the increased susceptibility to liver poisons occasioned by low protein intake appears to have a firm experimental basis.

This leads to the obvious question: If protection is afforded by raising protein intake from low to adequate amounts, can greater protection be obtained by increasing the levels of protein still higher? This question has not been studied as widely as it should, but the answer appears to depend on the nature of the toxic agent studied and perhaps on the type of pathology associated with its administration. Thus, Heppel and co-workers[140] found increasing protection for rats against 1,2 dichloroethane (ethylene dichloride) as the protein content increased from 4 per cent casein to 25 and then to 47 per cent. A similar type of relation between protein intake

and the toxicity of methyl chloride for rats was noted by Smith[141] when casein was tested at 9, 20, 25, and up to 35 per cent, above 35 per cent protection began to decrease. With other toxic compounds, such as emetine,[14] there is no further protective effect once the usual adequate level of protein is reached. However in the case of carbon tetrachloride poisoning, increasing the protein content above the minimally adequate level may even be deleterious.[143] The factor of renal damage in addition to liver damage in CCl_4 poisoning may be an explanation for this. Consequently, no all-inclusive statement can be made about the value of supra optimal protein intake.

This work on protein illustrates very well the need for caution in applying dietary findings with one toxic compound to others without first performing actual experiments. This point is further emphasized by studies on the effect of fat. It has already been stated that high levels of fat in the diet result in greater toxicity of chlorinated hydrocarbons even with adequate protein intake.[143] In the case of benzene when protein intake is adequate, increasing the fat content of the diet does not seem to have any deleterious effect on rats[44] and dogs.[145] Nor does fat level seem to influence appreciably the oral toxicity of either di- or tri-nitrotoluenes for growth of rats.[146–148] On the other hand, it has been found[146,148] that there may be *less* mortality to injected 2,4 dinitrotoluene among mice and rats subsisting on a high fat diet than among those on a low-fat diet.

With the large number of vitamins now characterized and the long list of toxic substances that can be tested there is obviously a huge amount of research that can be done in this field. However, relatively little research has been done on the influence of acute vitamin deficiencies on susceptibility to industrial poisons, while practically no work has been carried on with milder chronic deficiencies. More attention has been given to the effects of large doses of various vitamins given to animals already on normal diets before or after exposure to injurious agents.

Specific research cannot be discussed here because of space limitations, but it seems fair to state that the available evidence indicates that with severe vitamin deficiencies we may expect that often there will be a reduced resistance to toxic agents. Since ionizing radiations are becoming increasingly important in industrial work it should be mentioned that some evidence exists that deficiency of B complex vitamins in man[149] and in rats[150] predisposes to x-irradiation sickness.

The second major problem is this: Does exposure to toxic compounds increase the requirements for nutrients above the levels usually regarded as adequate? This is obviously a question of some importance but again we have to admit that the evidence from industrial experience is extremely meager; as regards animal experiments, there has been much less attention given to this problem than to the preceding one.

Before going on to discuss what has been done in this direction let us examine the question of the criteria that can be or have been, used in determining whether or not a toxic substance increases requirement. The most clear-cut criterion would be one where obvious deficiency symptoms occur upon exposure to the toxic compound, despite a nutrient intake that is considered adequate and where these symptoms are ameliorated by larger

amounts of the nutrient. Other criteria of actual or incipient deficiency are the findings of decreased blood or urinary levels of a particular nutrient or of evidence of a biochemical "lesion" associated with abnormal levels of some metabolic product, and where increased amounts of a nutrient are needed to restore conditions to normal. Basic to the validity of these criteria for increased requirement is the proof that the workers or animals studied have actually received adequate amounts of nutrients before and during exposure to the toxic agent. Deficiency symptoms or reduced nutrient levels which occur during or shortly after exposure and which may be ascribed to increased nutrient requirement may actually be caused by decreased intake due to deranged appetite.

Much has been written, primarily in European literature, purporting to show that exposure to benzene increases vitamin C requirement. Shils and Goldwater reviewed this literature[137] and concluded that the evidence does not convincingly support the claim, partly because the possible factor of diminished intake had not been ruled out.

The Council on Foods and Nutrition and the Council on Industrial Health of the American Medical Association, in their report entitled 'Indiscriminate Administration of Vitamins to Workers in Industry,'[151] have stated: 'It will doubtless be argued in certain quarters that in particular industries the workers may have a greater requirement for one or more vitamins because of the conditions of the employment. Certain distributors of vitamin preparations have been advocating that ascorbic acid (vitamin C) be administered as a prophylactic against poisoning by metals, organic solvents, aniline derivatives, phenol, cyanides, and so on. The scientific evidence offered at this time in support of such a practice is unsatisfactory.'

Increased nutritional requirements may occur as a result of one or more of the following conditions: (1) decreased absorption as a result of deranged gastro-intestinal function, such as diarrhea, vomiting, or damage to the pancreas or intestinal mucosa; (2) increased excretion of nutrients either in urine, sweat, or hemorrhage; (3) increased physiologic need such as may occur during pyrexia, hyperthyroidism, or for conjugation reactions of detoxication; (4) deranged or disturbed enzyme systems which may be overcome or by-passed in whole or in part by increased amounts of certain nutrients or metabolites; (5) inhibited synthesis of nutrients by intestinal bacteria such as may occur with prolonged ingestion of certain drugs such as sulfonamides or salicylates; and (6) impaired retention, metabolism or utilization of nutrients within the tissues such as may occur with liver damage, hypothyroidism, or anti-vitamins. While all of these conditions have been studied using experimental animals treated with a large variety of different drugs and toxins, relatively little is known of their occurrence in industrial situations with the exception of those already mentioned. That metabolic derangements not yet recognized may be occurring among workers exposed to chemicals is suggested in striking fashion when we recall that the marked effect of alcohol on individuals exposed to tetraethyl thiuramdisulfide ("antabuse") was first noted in workers in rubber manufacturing plants.[152]

Ershoff has pointed out[153] that many drugs impose a stress on the organ

ism, which calls for an adaptation and suggests that certain nutritional factors may prevent the occurrence of what Selye[154] termed "a state of exhaustion' and permit the continuance of the 'state of resistance "

A number of experiments indicate that certain vitamins given in large amounts to animals already on an adequate diet have little or no effect on resistance to industrial poisons for example ascorbic acid does not offset TNT toxicity[155–157], and pyridoxine[158] and liver extract[159] do not benefit the leukopenia of benzene poisoning Two studies made in American munitions plants during World War II failed to reveal any reduction in the incidence of symptoms of TNT poisoning among exposed workers as a result of consumption of multivitamin capsules [160,161] On the other hand, large amounts of para amino benzoic acid have been reported to decrease the toxicity of organic arsenic[16] and antimony[163] compounds More notably pyridoxine in individual doses of 25 to 100 mg has been found by many clinicians to prevent or ameliorate *x* irradiation sickness [164,165] Pretreatment with cysteine markedly reduced toxicity from the total body irradiation of mice and rats [166] The basis of the beneficial effect of these large doses of nutrients may well be pharmacologic rather than nutritional This certainly appears to be the case with cysteine in relation to irradiation since the sulfhydryl group of the amino acid acts to protect the sulfhydryl groups of certain essential enzymes [167]

In conclusion it may be stated that out of this contradictory and complicated subject at least four facts are clear

1 Various deficiency states, particularly that of protein and lipotropic compounds, often increase susceptibility to toxic substances hence in industrial situations emphasis must be placed on an over-all adequate diet

2 The claims for widespread increased requirements for certain nutrients by those exposed to toxic compounds do not rest on firm foundation With certain harmful substances or irradiation however, extra nutrients may be beneficial

3 We must be careful not to carry over evidence gained with one toxic substance and specific nutrients to other toxic substances and other nutrients without thorough investigation of each situation

4 To be more certain of nutritional facts that are to be applied to human beings, we must study human beings in their particular environment more thoroughly We must also plan our animal experiments so that basic conditions are as similar as possible to those existing in industry This means among other things that much greater emphasis should be given to the study of the effects of mild chronic deficiencies on the susceptibility to toxic agents

SOME PRACTICAL CONSIDERATIONS OF IN-PLANT FEEDING

Objectives — To supply to workers food that is (1) Nourishing Mid-shift meals should supply at least one-third of the daily nutritional needs Cooking procedures should maintain food value at optimum levels (2) Attractive The employees should want to eat the food on the counter

(3) Reasonably priced (4) Quickly served The worker should be aided in making the most of his lunch period (5) Eaten unhurriedly in surroundings that are comfortable, quiet, and attractive

Another objective is to utilize the in-plant feeding program to improve the food habits of workers and, through them, their families

Facilities, Operations and Personnel —The facilities for food preparation, service, and consumption are the basic factors The final decision as to type, size, and lay-out rests with top management and must take into account the policies on length of lunch hour, staggering of eating periods, finances, use of outside eating establishments and many related matters The problems of industrial feeding differ in certain respects from those of commercial eating establishments, consequently, facilities formulas and serving procedures used in the latter often do not meet industrial needs satisfactorily The design of good service and the selection of facilities are technical matters based upon definite principles Of fundamental importance is the concept of efficient flow in the preparation of food Analogous to systems used for mass production of many commodities, time and motion should be reduced to a minimum

A pioneer effort in facilities lay-out planning and design for this purpose was that of the Industrial Feeding Programs Division of the War Food Administration during World War II [168] The experiences gained during the industrial expansion in that war by management, food service managers, architects, and facilities manufacturers has had widespread post war effect in improving facilities and operations

The importance of speedy service to the workers would appear self evident The need for fast service has been so great in many installations that food quality and acceptance have suffered However slow service which is far more frequent, has been even more damaging to worker and management acceptance Slow service may be due in part at least to the short-sighted application of the long commercial-type cafeteria line with a large and diverse choice of foods Where large numbers must be fed in a short time there should be (1) A sufficient number of short serving counters requiring a minimum of labor (2) A limited choice of foods with daily menu changes to avoid monotony The introduction of a single price limited choice meal in industrial feedings has been very successful Such a meal consisting of an entree, two vegetables (one of which is a fresh green salad), beverage with or without dessert, allows large scale efficient puchasing, preparation and service, and insures a nourishing meal

In this connection it should be noted that an important contribution can be made toward the continuing consumption of nutritionally valuable foods by judicious price adjustments[169] or by incorporation of milk or ice cream, for example, in the single price meal

Food Preparation and Service —The "gentle art" of cookery can remove appreciable amounts of essential nutrients either by destruction or by solution in cooking waters which are then discarded Precautions should be taken to conserve nutritive value of foods by well-established procedures [170]

Constant vigilance must be exerted through the routine practice of sanitation measures to prevent spoilage and parasitic contamination of

room to accommodate this group who should be encouraged to use the facilities

Between-meal Supplements —Supplementary feeding should be regarded as an integral part of the whole dietary and the foods eaten should contribute to the daily requirements Emphasis should be placed on making available attractive and nutritious items such as fresh fruit, fruit and tomato-juices, milk and other dairy products and sandwiches with fillings of good protein, mineral, and vitamin content It should be a policy to discourage foods and beverages which contribute little but calories

Nutrition Education —In-plant feeding is only a part of the answer to the nutritional problems of industrial workers, since those individuals who patronize the service usually eat only one meal there and the majority of workers do not have or do not utilize such food services The larger problem remains of insuring adequate nutrient intake on a daily basis, regardless of where the food is prepared and consumed, not only by the worker, but also by all members of his family This type of program has been attempted by only a few companies so far as we are aware and documentation of its effectiveness is lacking There have been, however, more limited educational programs carried on among employees Some of these indicate that the industrial feeding service offers a unique and fruitful opportunity for improving the food selection of adults [172] Though such educational activities are directed towards the employees it has been found that there is an extension of the improved food habits into the home [172] It should be emphasized that in order to be effective, there must be an imaginative and personal appeal in a long-range campaign, simply distributing pamphlets or displaying incidental posters will have relatively little effect

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Chapter 38

Principles of Emergency Feeding

By Robert S Goodhart

By "emergency feeding" is meant the supplying of food or meals to persons made destitute, or otherwise deprived of access to food or meals, by either natural or man-made catastrophe, for such time as it may take to relocate or hospitalize such persons and to re-establish normal channels of trade Emergency feeding includes also the supplying of food and meals to the multitude of workers required for the care of the injured the clearing of debris, fire-fighting duties, policing, and all other activities essential for recovery from catastrophe

For an effective emergency feeding program, it is essential that the purposes of the program be clearly understood These may be one or several, depending upon the nature and duration of the catastrophe upon the population involved and upon what it is hoped to accomplish with and for that population[2]

In the instance of an enemy attack, the primary immediate purpose would be the maintenance of morale and the avoidance of panic[3] For this reason it is essential that the emergency feeding program be so designed that it can be put into effect promptly and be operated efficiently with a minimal amount of professional help and equipment Simplicity of design and organization with a clear and direct line of authority at all levels of operation, are essential It is necessary also that the full resources of the community, in materials equipment and personnel, be properly utilized In disaster, food and feeding are basic morale factors and often determine recovery from disease and injury As succinctly stated by Colonel J H Simmons,[1] "Foregoing a bit of our culture and comforts and getting down to basic essentials, we realize that the first necessities after a disaster will be water, food and shelter

It is important that adequate provisions be made for the care and feeding of pregnant and lactating women and small children, not only because the future of the people depends upon the health of these groups, but because assurance of their receiving necessary care and food will do a great deal to bolster morale and prevent panic Special arrangements must also be made for the feeding of the sick and injured to permit recovery Lastly, since the work output of persons engaged in strenuous work deteriorates markedly when they are furnished inadequate or unpalatable food, provision must be made to assure the satisfactory feeding of essential workers

As pointed out by Hundley[3] in feeding the normally healthy, uninjured person four years of age or over excluding pregnant and lactating women and essential workers the food provided should be primarily designed to

allay hunger and sustain morale, rather than to fit any rigid nutritional standard Most authorities attach considerable importance to the service of hot beverages, soups or stews as soon as possible after a catastrophe, because of the beneficial effect of such foods on morale Under the conditions of the usual type of disaster, and according to the general Civil Defense plan, it is considered unlikely that any one individual will be dependent on emergency feeding for longer than 14 days and in no instance longer than thirty days[3] A bulletin (TB-5 3) of the Office of Civil and Defense Mobilization suggests "the advisability of planning for a two-week occupancy (of family shelters), even though in many areas radiation levels may permit leaving shelter after two or three days"[4]

The Food and Nutrition Board of the National Research Council[5] has pointed out that "It should be appreciated that drastic reduction of intake for a few days, or even weeks, is tolerated except by infants, by lactating women, by the sick and injured, and by those engaged in heavy physical work, particularly if the calories that are available come primarily from foods that furnish a variety of nutrients, such as bread, potatoes, and milk, in contrast to foods such as sugar, syrups, and oils, which supply primarily calories" (Some modification of this statement may be indicated at least in regard to oils, since it has been shown that dietary fat has a protective effect against irradiation injury, in the rat[6,7] A high fat-high protein, 1,000 calorie ration (pemmican) has been found to be adequate "for most survival situations faced by air crews in the Arctic"[8,9])

"If emergency feeding must be continued for more than a few weeks, the problem of individual nutrients, as well as of calories, assumes importance, cognizance must be taken of needs for protein, thiamine, other B-complex vitamins, and ascorbic acid Provision of minerals and fat soluble vitamins does not become a problem unless food shortages have persisted over several months"

In this same report of the Food and Nutrition Board[5] it is stated that "on the basis of present knowledge, possible contamination of foods and water by atomic radiation is negligible, except for foods unprotected in any way and apt to receive dust carrying radiation Any goods kept in containers or wrappers, or having a protective skin, such as fruits and potatoes, will not become contaminated with radiation and may be safely used when the protective covering or skin is removed" In regard to the water supply, Simmons[1] points out that "In every home, in every eating establishment, and in many office buildings there are excellent sources of emergency water supply—sources which in the confusion of disaster we are apt to forget even though they are close at hand Water in bottles in the refrigerator and from melted ice cubes is perfectly safe and protected Water-packed canned fruits and vegetables will also provide a good source of water The home water heater, which usually contains at least 25 gallons of water, can be drained by opening a tap at the bottom"

Nutritional requirements for periods of two weeks or less are both quantitatively and qualitatively less than allowances for longer periods Many of the essential nutrients are stored in the body to a considerable extent In this category are the essential minerals, all the fat-soluble vitamins, ascorbic acid, and all the B vitamins that we know anything about, with

the possible exception of thiamine Essential for short periods of time are water, energy, protein and possibly thiamine Thiamine is the only micronutrient a deficiency of which has been shown to produce symptoms in man within a period of less than one month For the first few days of an emergency, only one nutrient can be regarded as essential for the survival of the individual, and that one is water This is a fact which must not be overlooked in planning emergency rations Dehydrated and concentrated foods may save storage space, but they are worse than useless in the absence of potable water The mainstays of the emergency food locker might well be *unconcentrated* canned tomato and citrus fruit juices soups stews, fruits and vegetables The water contained in these items may be life saving

The Office of Civil Defense Mobilization Ad Hoc Advisory Group on Research and Development for Food for Shelters, in its report of March 18, 1959, to the Food and Nutrition Board of the National Research Council has suggested minimal nutritional allowances for shelter rations (Table 146) representing "the average per capita levels of intake which will assure the maintenance of health for the population, and based on the U S population census of July 1, 1958 The purpose of these nutritional allowances is to serve as a guideline in the planning of shelter rations to insure that the rations planned will at least meet these minimal allowances It does not prescribe that the rations need to be this restricted Currently the OCDM is using a 2000 calorie level for operational planning purposes Similarly New York City has calculated minimal nutritional requirements based upon the estimated population distribution in the City of New York [2] The recommendations of these two groups are not far apart except in the case of thiamine where the Advisory Committee on Emergency Feeding to the New York City O C D specifies a thiamine requirement for short-term emergency feeding The Office of the Surgeon General, U S Army also has proposed minimal nutritional allowances per capita per day (Table 147)

After considerable study of the food supply and distribution situation in New York City, and of the city s facilities and utilities, the Advisory Committee on Emergency Feeding to the New York City Office of Civil Defense recommended the following nutritional and food allowances for short term emergency feeding [2]

NUTRITIONAL ALLOWANCES FOR EMERGENCY PERIODS UP TO TWO WEEKS

For Evacuees —An evacuee is defined as a normally healthy uninjured person four years of age or over, excluding pregnant and lactating women who is not engaged in essential emergency work

Energy	1 600 cal
Protein	35 gm
Thiamine	1 mg
Water	1 qt

The daily allowance of 1 600 calories and 35 gm of protein is about the minimum necessary to prevent excess body protein destruction 1 0 mg

of thiamine daily is the recommendation of the National Research Council for adults on diets containing less than 2,000 calories

Menus for this group should be devised to meet the following conditions (1) No fuel—no water, (2) water and fuel, (3) fuel—no water, (4) water—no fuel

The largest component of all the menus might well be bread Enriched white bread made with 4 per cent nonfat milk solids will supply, per pound energy, 1,250 cal , protein, 38 gm , thiamine, 1 1 mg

TABLE 146 —SUGGESTED MINIMAL NUTRITIONAL ALLOWANCES FOR PLANNING RATIONS FOR SHELTERS

Levels of Nutrients as Consumed Per Capita Per Day for Ration Planning

	Survival Only[1]		
	2 Weeks	*4 Weeks*	*8 Weeks*
Water	1 Quart	1 Quart	1 Quart
Calories	1500	1500	1500
Protein gms		35	35
Thiamine mg			0 4

	Austere[2]	*Near Normal*
	(For Periods up to 8 Weeks)	
Water	2 Quarts	1 Gallon[3]
Calories	1800	2000
Protein gms	50	65
Calcium, gms	0 3	0 4
Vitamin A, I U	2000	3000
Thiamine mg	0 4	0 6
Niacin, mg	5	8
Vitamin C mg	10	30
Riboflavin mg	0 7	1 0
Iron mg	0 7	9 0

[1]To meet sheer physiological needs Special supplemental foods to be included for infants pregnant and lactating mothers and the injured

[2]To meet physiological and psychological requirements

[3]Includes water for cooking and drinking

One pound of bread will provide three-fourths of the emergency energy allowances and all the emergency protein and thiamine allowances for normal people not engaged in essential emergency work In addition 1 pound of enriched white bread made with 4 per cent milk solids supplies 359 mg of calcium, the equivalent of 10 oz of milk, 8 0 mg of iron, 0 7 mg of riboflavin, and 10 mg of niacin If bread only is available then sufficient nutrients in an acceptable form to sustain life and morale for a period up to two weeks can be supplied by 1½ pounds of bread daily However, the menus are planned to consist of 1 pound of bread plus about 400 calories from other safe, locally available foods It is stressed that these nutritional allowances are minimal and it is expected that they will be exceeded in most instances

TABLE 147 —PROPOSED (U S Army TM 8-501 revised edition) MINIMAL NUTRITIONAL ALLOWANCES

Recommended Time Limit	per Capita per Day		
	Phase I *2 Mo*	*Phase II* *6 Mo*	*Phase III*[1] *1 Year*
Calories	1500	1900	2200
Protein gm	35	50	65
Calcium gm		0 3	0 4
Vitamin A I U[2]		2000	3000
Thiamine mg	0 4	0 4	0 6
Riboflavin mg		0 7	1 0
Niacin mg		5	8
Vitamin C, mg		10	30
Water	1 quart		

[1]Time phases are based mainly on caloric considerations indicating that limit beyond which a body weight loss of 10% may be expected
[2]Not less than 10% from animal sources

For Essential Workers —Essential workers should be given a meal every four hours, while working The allowances per meal have been set as follows

Energy	1 400 cal
Protein	25 gm
Thiamine	0 875 mg
Water	4 qts (daily)

Menus need to be devised for the following conditions (1) No fuel—no water (2) water and fuel (3) fuel—no water (4) water—no fuel

As in the feeding of evacuees, dependence is placed upon bread, but margarine is added The remaining calories are to be obtained from other foods, depending upon the availability of individual food items Packaged Army emergency rations could be used if available

For Vulnerable Groups, Other Than the Sick and Injured —These include infants children under four years of age and pregnant and lactating women The minimal daily allowances for emergency periods up to two weeks have been set as follows

	Energy	*Protein*	*Thiamine*
Infants up to 6 months	110 cal /kg	3 2 gm /kg	0 4 mg
Pregnant women	2 400 cal	80 gm	1 2 mg
Lactating women	3 000 cal	95 gm	1 5 mg
Children 6 months to 4 years	1 200 cal	35 gm.	0 6 mg

The essential difference between the menus for this group and for evacuees is in the milk allowance The milk priority is as follows

Group 1 —Infants pregnant and lactating women
Group 2 —Children 6 months through 3 years
Group 3 —Children 4 years and over

For the Sick and Those with Minor Injuries—All the usual therapeutic and special diets are to be discontinued For example, the diabetic will depend upon insulin alone, the peptic ulcer patient on antacids, and the colitis patient upon anti-diarrheal preparations These groups will receive three simple meals each day containing the following daily allowances

Energy	2,200 to 2,500 cal
Protein	85 to 100 gm
Thiamine	1 5 mg
Water	Up to 3 qts

For the Severely Injured and Burned Patients—*When the nutritional* requirements are modified by disease, injury, or burns, the maintenance of an optimal balance of electrolytes and fluids during the first twenty four hours often determines survival The daily allowances for this group are

Energy	3 500 cal
Protein	150 gm
Thiamine	3 mg
Water	4 to 12 qts

To meet these high allowances a high protein, high calorie liquid supplement is recommended

FORMULA 1

Dry skim milk powder	350 gm
Fluid whole milk	730 ml

The approximate composition of this formula is carbohydrate 217 gm, protein 150 gm fat 32 gm, thiamine 1 5 mg, total calories 1,760, volume, 1,000 ml

FORMULA 2

Dry skim milk powder	1 lb (16 oz)
Evaporated milk	1 large can (14 5 oz)
Water	14 5 oz

The approximate composition of this formula is essentially the same as that of Formula 1

In the event that fluid milk or evaporated milk is not available water can be substituted in Formula 1 for the fluid milk component The approximate composition of this formula is carbohydrate 182 gm, protein 125 gm, fat 3 5 gm, thiamine 1 22 mg total calories 1 260, volume, 1,000 ml

These high calorie, high protein liquid supplements may be modified by locally available dessert-type flavorings When high fluid intakes are indicated they may be diluted with water or other permitted liquids When used for tube feedings or when low potassium intakes are prescribed they cannot be diluted with fruit juices If refrigeration is not available, no more than a six-hour supply should be prepared

If the patient is able to eat the prescribed diet, he will receive the diet plus approximately three 8-oz glasses of the supplement If he is unable to eat the regular diet, he will receive approximately 2½ qts of the supple-

ment daily by mouth (or by stomach catheter if necessary), plus additional water, salts and vitamins as required

Most of the menus recommended for emergency feeding in New York City are based upon the use of bread as the major component of the diet In addition, the plans depend greatly upon the use of available customary foods

The Advisory Committee also has recommended that New York City families maintain certain food reserves in the home against the possibility of a war caused emergency These recommendations were based upon a *post catastrophe situation in which the great need will be for water, to a* lesser extent calories, where there well may be no opportunity for heating foods or water, and where there will be a good chance that glass containers will be smashed waxed paper packages burst, and uncanned foods in general contaminated Taken into consideration, also, were the facts that foods for the emergency food shelf must be stable without refrigeration (excludes cheese), should be as nutritious and economical as possible (canned tomato and citrus fruit jucies are much to be preferred to canned non citrus fruits and vegetables on both counts), and should not unduly increase thirst (excludes canned ham canned corned beef, canned tuna, salted crackers and soft drinks)

This author is *very strongly of the opinion that the* Food Reserve Shelf should not be designed or promoted to cause the hoarding of food, the development of markets for special products or to provide an outlet for agricultural surpluses The reserve shelf which follows, is to a considerable extent compatible with a normal, efficient household purchasing program

FOOD RESERVE SHELF

A That families, in so far as storage and refrigeration space are availa[illegible] market on a two day to a week basis rather than daily

B That each family keep on its 'reserve shelf a supply of family [illegible] liked *foods, to be kept fresh by rotation through normal use* It is [illegible] sized that these foods will not keep indefinitely They will be go[illegible] several months Freshness and economy will be guaranteed if th[illegible] used as part of the regular food supply whenever any item is ta[illegible] the 'reserve shelf it should be replaced on the next market d[illegible] suggested "reserve' shelf is as follows

1 *Dry Skim Milk* —1 lb (2 lb if family is over 4 persons)

2 *Evaporated Milk* —One 14½ oz can (2 cans if family is over 4 [illegible] for each child under 4 years of age and each pregnant or [illegible] increase inventory by two 14½ oz cans)

3 *Citrus* —One No 2 can (not frozen or concentrated) of any one [illegible] for each member of the family

Grapefruit juice	Mixed orange grapefru[illegible]
Orange juice	Tangerine juice
Tomato juice	Canned grapefruit sec[illegible]
Canned tomatoes	Mixed orange and gra[illegible] sections

4. *Soup.*—One No. 2 can of any ready-to-serve soup (any variety except clear consomme or bouillon) for each member of the family.
5. *Main-dish Foods.*—One No. 2 can of any of the following for each member of the family:
   - Spaghetti, macaroni, ravioli with meat balls or meat sauce
   - Baked beans, kidney beans, lima beans
   - Sweet potatoes, white potatoes
   - Corned beef hash, meat and vegetable stew
   - Chile con carne with beans
   - Salmon (large can)
6. *Crackers.*—(Unsalted) 1 lb. tin container.
7. *Bread Spreads.*—One jar or can of one of the following for each member of the family:
   - Jelly, jam, marmalade
   - Fruit butter, peanut butter
8. *Water.*—One gal. container of tap water (2 1-gal. containers if family is over 4 persons).

Desirable Nonfood Items

1. 3 cans of "canned heat"
2. 1 can opener
3. 1 box of safety matches
4. Candles and holders
5. Paper cups, plates, spoons and forks

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TABLE 148.—COMPARISON OF RADIOISOTOPES IN ENVIRONMENTAL CONTAMINATION

	Iodine-131	*Barium-140*	*Strontium-89*	*Strontium-90*	*Cesium-137*
Physical half life	8 days	13 days	51 days	28 years	30 years
Metabolic behavior	collects in thyroid	like calcium collects in bone	like calcium collects in bone	like calcium collects in bone	like potassium collects in muscle
Removal rate from body	fast	slow	slow	slow	relatively fast
Main pathways in food chain*	A → V → C → M → Man; A → Man	A → V → C → M → Man	A → S; A → V; S ⇄ V; V → C → M → Man; V → Man		A → V → C → M → Man; C → MP → Man
Samples for monitoring radioisotope levels	vegetation milk, and thyroid	vegetation and milk	soil, vegetation milk dairy products bone and aquatic food	soil vegetation, milk dairy products bone and aquatic food	vegetation, milk, dairy products, meat and whole body
Maximum permissible radioisotope concentrations, μμc per liter†	3 000	200 000	7 000	80	150 000
Radioisotopes in milk, μμc per liter‡	121	12	52	6 4	57
Comparative radiation dose to humans rad	<0 01 to thyroid in 1955 and 1956	<10% of strontium 89 dose	approximately from 1 to 20% of strontium 90 dose	approximately 0 2 to 0 4 to skeleton over 70-yr period from present tests§	approximately 0 001 per year from present levels

*A = atmosphere V = vegetation M = milk S = soil C = cattle MP = meat products

†Recommended maximum permissible concentrations for specific radioisotopes in drinking water as derived from recommendations of National Committee on Radiation Protection and Measurements These concentrations and milk values are quoted by Public Health Service

‡Levels found in United States from July 1957 to July 1958

§This estimation includes recent analytical data and concepts of nonuniform stratospheric inventories developed at May 1959 congressional subcommittee hearings

longer half life, becomes more dominant with time The strontium radioisotopes, of course, are cumulative in bone Cesium-137, which follows potassium in metabolism, is considered less of a hazard than strontium-90 because it is turned over relatively rapidly in the body, it is not selectively concentrated in any one part of the body, and it does not pass appreciably from soil to plant in the food chain

Radioactive contaminants are transferred to man by means of specific pathways through the main terrestrial food chains These food chains are illustrated diagrammatically in figure 75 and the primary pathways of barium, iodine, strontium and cesium are shown in Table 148 As an example, strontium 90 is deposited from the atmosphere on the foliage of

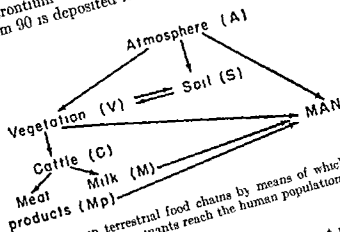


Fig 75 —Diagram of main terrestrial food chains by means of which environmental radioactive contaminants reach the human population

plants and on the soil Transfer between soil and plant proceeds in both directions by normal root uptake and by washing from leaves or death of leaves Strontium 90 reaches the human body by direct consumption of vegetation and of milk from animals that have fed on the vegetation

The relative importance of the various pathways depends on many factors for example the composition of the soil (calcium level) and the nature of plant cover A heavy root mat will tend to trap fall out strontium and delay its reaching the soil for dilution with soil calcium while at the same time permitting absorption into the plant from the base of the stem The agricultural management of crops and livestock which includes the plowing depth fertilizer practice and type of feeding (barn or pasture) employed, is another factor to be considered Also of great importance are dietary habits of the population and food technology As an illustration in the processing of frozen vegetables washing them prior to freezing will remove some of the surface contamination If nuclear tests are stopped the soil reservoir will become increasingly important therefore the time pattern of contamination has to be taken into account Although food chain considerations are extremely complex certain generalizations can be made It is obvious that the pathways that require considerable time in passage to man (for example via the soil) are of no significance for the short lived radioisotopes iodine-131 and barium-140 It also appears that the present contamination of diets originates mainly from surface contamination rather than from the soil reservoir

The movement of strontium radioisotopes from soil to man is interrelated and, to some extent, governed by the simultaneous movement of calcium. In all steps of the food chain from vegetation to human bone, calcium is preferentially utilized relative to strontium. Thus, it has been calculated that at equilibrium the strontium calcium ratio in bones of young infants would be from 3 to 12 per cent of that in vegetation, with values of 8 to 16 per cent in the bones of persons over 6 months of age. Although milk is our primary source of calcium, the discrimination against strontium relative to calcium in passage from the feed of the cow to its milk tends to reduce the importance of milk as a source of strontium-90. While dai products furnish some 80 per cent of our dietary calcium, they may suppl somewhat less than 40 per cent of the total strontium 90 intake whe steady-state conditions are established. Attention should also be give to contaminated water supplies as a possible source of strontium 90. In making estimations, the entire strontium 90 and calcium intake of the population must be considered.

The soil reservoir probably will not be an important factor for cesium-137 because of the fixation of this element in the soil and its consequent un availability to the plant. At the present time, about 60 per cent of the cesium-137 content of the average diet is derived from dairy products, 25 per cent from meat products, and the remainder from vegetables, cereals, and fruits.

RADIOISOTOPE LEVELS

The present levels of these radioisotopes in the biosphere (soil plants animal products man) can be determined with reasonable accuracy by radiochemical analysis. For purposes of illustration Table 148 presents some of the average radioisotope values for milk in the United States for the years 1957 and 1958. In the early part of 1959, values for strontium 90 in milk from various locations in the United States all averaged well under 30 micromicrocuries (μμc) per liter. These values are below the recommended maximum permissible limits for lifetime exposure to specific radio-isotopes in water. Discussion of maximum permissible levels is beyond the scope of this paper. It is urged, however, that scientists and laymen should develop a clear understanding of what is implied by figures given as maximum permissible levels and how these figures are derived.

Dietary levels of strontium 90, which are expressed as micromicrocuries of strontium-90 per gram of calcium, have been estimated at approximately 0 4 2, 4 5 and 7 for each year from 1953 to 1957 respectively. It is estimated that the maximum levels from tests to date will occur from 1962 to 1965 and that the average maximum level in the diet of persons living in the United States at that time may reach about 24 μμc of strontium 90 per gram of calcium. Recent considerations indicate that much of the present strontium-90 in milk may not have come through the soil but found its way into the plant by foliar absorption or other processes. This has important implications (*a*) if there is no further testing the levels may fall fairly rapidly, (*b*) the contamination of food when only the soil route is operative should be much lower than at present, and (*c*) this would explain

why levels in non milk foods are not greatly higher than in milk foods as is expected because of the dairy cow's preferential use of calcium

Milk from numerous areas has been analyzed to determine the local variation in dietary levels of strontium 90 The highest values observed were about five times the mean value, while milk from cows fed on vegetation grown in low calcium soils were approximately twice the mean value There appears to be less variation in the levels found in the human population presumably because the individual consumes food that originates from many areas It is not yet possible, however, to express variability in precise statistical terms

The most direct and important evidence comes from analysis of tissue samples from the human population Typical values calculated and expressed in terms of radiation dosage rather than concentration of radioisotopes, are given in Table 148 A scale of values to indicate expected response of man to radiation is presented in Table 149 It can be noted that present and anticipated levels of radioactivity in man based on the effects of nuclear tests to date, are below those known to produce any observable effects However, indiscriminate testing of nuclear weapons, either by many nations or at higher rates could lead to levels of strontium-90 in the food chain that would be of definite concern The most difficult issue, particularly because of its moral overtones is whether present levels (also of carbon 14)[3] will produce absolutely no incidence or will produce finite incidences of genetic or somatic harm in the world population This is a complex and controversial matter relating to linearity of response and patterns of threshold versus non threshold behavior at low levels

TABLE 149 —EFFECTS OF RADIATION ON MAN

Radiation Dose, rad	*Source and Conditions*	*Observations*
3 000-6 000	3 6 µc radium or x radiation to skeleton	Bone sarcoma
300	0 4 µc radium	Minimal nondeleterious bone changes
90	0 1 µc radium	No observable effects
50-60	(suggested as levels that would double leukemia incidence)	
7-15	Natural background	No observable effects
10	(recommended upper limit of radiation from any man made source)	
0 2-0 4	(estimated dosage from strontium 90 from tests to time of writing)	
0 05	(estimated dosage from cesium 137 from tests to time of writing)	

Low level monitoring, which detects excess radiation before health hazard levels are reached, will become important as a public health function to give advance warning of any peacetime operational difficulties Public reassurance will be provided by monitoring at natural radiation levels before and after nuclear installations are placed in operation

SUMMARY

Although at the present time there is no indication for a change in our dietary habits, broad-scale research on the problem of radioactivity in foods and its implications must continue for future public welfare Even if testing of nuclear weapons is halted, peacetime applications of atomic energy will release some radioactive materials into the environment Therefore close supervision of the dietary levels of radioisotopes and understanding of possible effects on man are necessary for evaluation of atomic energy benefits versus biological cost

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Appendix B

A DAILY FOOD PLAN*

Criteria of an adequate diet are considered in Chapter 18 To obtain the needed nutrients described in this Chapter one must eat the amounts suggested from each of the "basic" four types of foods The "basic" seven, a guide to meal planning for many years, includes fats and sugars, and separate fruits and vegetable categories Fats, oils and sugars, though still essential in the diet, are not considered as separate groups in meal planning because they are eaten in combination with appropriate foods any way, and they contribute mainly calories

TABLE 150 —FOUR GROUPS OF FOODS

1 Milk group Some milk daily—

Children	3 to 4 cups
Teen-agers	4 or more cups
Adults	2 or more cups
Pregnant women	4 or more cups
Nursing mothers	*6 or more cups*

Cheese and ice cream can replace part of the milk

2 Meat group 2 or more servings—
Beef, veal, pork, lamb, poultry, fish, eggs, with dry beans and peas and nuts as alternates

3 Vegetable fruit group 4 or more servings, including a dark green or deep yellow vegetable important for vitamin A —at least every other day
A citrus fruit or other fruit or vegetable important for vitamin C-daily
Other fruits and vegetables including potatoes

4 Bread-cereals group 4 or more servings—*Whole grain*, enriched, restored

The minimum number of servings given in Table 150 constitute a foundation for an adequate diet The amounts of servings from each food group provide the minimum but not all of the nutrients needed for optimum nutrition To achieve the latter goal, greater amounts of these foods will have to be used, also items not specified in the four categories of foods, such as, butter, margarine, other fats, oils, sugars and unenriched, refined grain products will complete the caloric needs All of the needed Vitamin C is supplied by the minimal amounts of fruits and vegetables (fresh, frozen or canned) given in Group 3 Thiamine, riboflavin and niacin are supplied by foods from all four categories, especially when additional servings of these foods are eaten to meet caloric needs Vitamins B_6, B_{12}, Folic Acid, Panthothenic Acid and Biotin are generally held to be adequately supplied by the foods listed in the four categories To quote from Goodhart "It

*We are indebted to the Institute of Home Economics Agricultural Research Service, for permission to use material from publication Essentials of an Adequate Diet, Home Economics Research Report No 3 1957 United States Department of Agriculture

must be emphasized that these allowances are designed for the maintenance of good nutrition of healthy persons in the United States of America Many healthy individuals require less than the recommended allowances and some apparently healthy persons require more The Recommended Daily Dietary Allowances do not apply to persons suffering from disease, metabolic disorders and injury, and are not to be used as standards for hospital diets"

TABLE 151 — CALORIC VALUES FOR A FEW SELECTED FOODS

	Amount	*Calories*
Apple	1 medium	75
Bacon	1 slice	50
Banana	1 medium	90
Bread	1 slice	65
Butter or margarine	1 teaspoon	35
Cake, iced	1 piece 3 by 2 by 1½ inches	290
Carrotts, cooked	½ cup	20
Cheese, cheddar	1 ounce	115
Eggs	1 egg	75
Hamburger, cooked	3 ounces	315
Lettuce	1 large leaf	5
Luncheon meat	1 slice	85
Milk, skim	1 cup	85
Milk, whole	1 cup	165
Oatmeal, cooked	½ cup	75
Orange juice	½ cup	55
Pie two crust	4-inch sector (9 inch diameter)	325
Pork chop	1 medium	295
Potato	1 medium	100
Salad dressing	1 tablespoon	60
Sugar, sirup, jam	1 tablespoon	60
Tomato	1 medium	30

Development of a Day's Meals

Menu for 5-year-old child

Breakfast

*Orange	1 medium
*Oatmeal	⅓ cup
Sugar	1 teaspoon
*Milk, whole	1 cup
*Toast, enriched	1 slice
Butter or margarine	1 teaspoon

Lunch

*Creamed tuna fish	½ cup
*Toast, enriched	1 slice
*Carrot strips	⅓ medium carrot
Fruited gelatin	⅓ cup
Cooky	1 medium
*Milk, whole	½ cup

Dinner

*Beef pot roast	1½ ounces
*Mashed potatoes	¼ cup
*Green peas	¼ cup
Celery	1 medium stalk
*Bread, enriched	1 slice
Butter or margarine	1 teaspoon
Applesauce	½ cup
*Milk, whole	½ cup

Between meal snack

*Milk, whole	½ cup
Banana	1 medium

Menu for 15-year-old boy

Breakfast

*Orange	1 medium
*Oatmeal	⅔ cup
Sugar	1 teaspoon
*Milk, whole	1½ cups
Egg	1 egg
Toast, enriched	2 slices
Butter or margarine	1 teaspoon
Jelly	1 tablespoon

Lunch

*Tuna fish sandwiches	1½ sandwiches†
*Carrot strips	⅔ medium carrot
Tomato wedges	1 small tomato
Banana	1 medium
Cooky	1 medium
*Milk, whole	1 cup

Dinner

*Beef pot roast	4 ounces
*Mashed potatoes	⅔ cup
*Green peas	⅔ cup
Celery	2 medium stalks
Bread, enriched	1 slice
Butter or margarine	1 teaspoon
Apple pie	1 or 9 inch pie
*Milk, whole	1 cup

Between meal snack

*Milk	1 cup
Apple	1 large
Cookies	2 medium

*Starred items make up the minimum number of servings suggested from groups of the daily food plan

†Made with 3 slices white enriched bread, 2 ounces tuna fish, 2 tablespoons mayonnaise 2 leaves lettuce

TABLE 152.—CONTRIBUTION OF COMMON FOOD CHOICES, SELECTION I. NUTRIENTS PROVIDED BY COMMON CHOICES FROM EACH GROUP OF THE DAILY FOOD PLAN[1]

Food	*Amount*	*Food energy*	*Protein*	*Calcium*	*Iron*	*Vitamin A value*	*Thiamine*	*Riboflavin*	*Niacin*	*Ascorbic acid*
		Cal	*Gm*	*Mg*	*Mg*	*I U*	*Mg*	*Mg*	*Mg*	*Mg*
Milk, cheese, ice cream										
Milk, whole	1¾ cups	290	14 9	504	0 4	680	0 16	0 74	0 5	5
Ice cream	½ cup	145	2 8	88	Trace	370	03	14	Trace	Trace
Meat fish, poultry eggs, dry beans and peas nuts										
Ham cooked	3 ounces	340	20 0	9	2 5	0	46	18	3 5	0
Eggs	1 egg	75	6 1	26	1 3	550	04	13	Trace	0
Vegetables and fruits										
Carrots, cooked diced	½ cup	20	4	19	4	9 060	04	04	4	3
Orange juice fresh	½ cup	55	1 0	24	2	230	10	03	3	61
Potatoes mashed, milk added	½ cup	80	2 2	26	6	20	08	05	8	7
Applesauce canned sweetened	½ cup	90	2	5	5	40	02	02	Trace	2
Bread and cereals										
Bread white, enriched	3 slices	190	6 0	54	1 2	0	18	12	1 5	0
Oatmeal, cooked	½ cup	75	2 7	10	8	0	11	02	2	0
Total		1 360	56 3	765	7 9	10 950	1 22	1 47	7 2	78

[1]Source of data B K Watt and A L Merrill Composition of Foods—Raw Processed Prepared U S Dept Agr Agr Handb 8 1950

TABLE 153 —NUTRIENTS FURNISHED BY DAILY FOOD PLAN AVERAGE QUANTITY OF NUTRIENTS PROVIDED BY MINIMUM NUMBER OF SERVINGS SPECIFIED FROM EACH FOOD GROUP OF THE PLAN AND RECOMMENDED DAILY ALLOWANCES FOR THESE NUTRIENTS*

Food	*Amount*	*Food energy*	*Protein*	*Calcium*	*Iron*	*Vitamin A value*	*Thiamine*[1]	*Riboflavin*[1]	*Niacin*[1]	*Ascorbic acid*[1]
		Cal	*Gm*	*Mg*	*Mg*	*I U*	*Mg*	*Mg*	*Mg*	*Mg*
Milk, cheese, ice cream Milk equivalent[2]	2 cups	320	16 0	514	0 3	870	0 13	0 69	0 4	Trace
Meat fish, poultry, eggs dry beans and peas, nuts Meat equivalent[2]	4 ounces cooked	105	27 1	47	4 6	930	33	40	6 0	0
Vegetables and fruits[3]										
Dark green and deep-yellow vegetables[4]	¼ cup	25	1 0	23	6	2,590	04	04	3	13
Citrus fruits	½ cup	55	9	27	4	140	08	03	3	53
Other vegetables	½ cup	80	2 3	22	8	80	07	05	9	13
Other fruits	½ cup	80	8	16	7	560	04	05	4	7
Bread and cereals[1] Whole grain, enriched, restored	4 servings	290	8 8	55	2 1	30	30	16	2 5	0
Total		1,255	56 9	704	9 5	5,200	99	1 42	10 8	86
Recommended dietary allowances[5]										
Men (U S average)		2,700	75 0	800	12 0	5 000	1 40	1 90	14 0	75
Women (U S average)		1 900	60 0	800	12 0	4 000	1 00	1 50	10 0	70
Average adult		[illegible]	[illegible]	800	12 0	4 500	1 20	1 70	12 0	73

[1]Some cooking losses deducted

[2]Based on group averages in which nutritive values of individual foods are *weighted by proportions* in which they were used by U S urban families, 1948

[3]Based on group averages derived from nutritive value of the U S per capita food supply 1952–53

[4]Values used are a day s share based on $3\frac{1}{2}$ servings weekly—equivalent to a serving every other day

[5]Allowances for an average U S man and woman have been *adapted from* the National Research Council s recommended dietary allowances (1953) for the 45-year old man and woman These allowances were adjusted upwards to conform with the height of the average American of this age, and *calories* (and related nutrients) were adjusted downwards to conform with activity and environmental temperature typical for this country Basis for these adjustments are discussed in Applying 1953 Dietary Allowances to U S Population Groups C LeBovit and H K Stiebeling Jour Amer Diet Assoc *33*, 219–224 1957 The values shown for an *average adul* are averages of these adjusted allowances weighted by the proportion of men and women in this country 35 to 54 years of age For 1958 revision of Dietary Allowances see Chapter 18, page 532

[6]The amounts of foods listed represent the minimum nutrients supplied by these servings To make up the caloric shortage and supply of the additional nutrients needed for a complete diet it will be necessary to supplement additional servings of these same kinds of foods combined with fats and sugar used in cooking or at the table

TABLE 154 —CONTRIBUTION OF COMMON FOOD CHOICES, SELECTION II NUTRIENTS PROVIDED BY COMMON CHOICES FROM EACH GROUP OF THE DAILY FOOD PLAN[1]

Food	*Amount*	*Food energy*	*Protein*	*Calcium*	*Iron*	*Vitamin A value*	*Thia mine*	*Ribo-flavin*	*Niacin*	*Ascorbic acid*
		Cal	*Gm*	*Mg*	*Mg*	*I U*	*Mg*	*Mg*	*Mg*	*Mg*
Milk cheese, ice cream										
Milk, evaporated	¼ cup	85	4 4	153	0 1	250	0 03	0 23	0 1	1
Cheese, cheddar	2 ounces	225	14 2	412	6	800	02	24	Trace	0
Meat, fish, poultry, eggs, dry beans and peas, nuts										
Beef, hamburger, cooked	1 ounce	105	6 3	3	8	10	02	05	1 4	0
Dry beans, cooked	1⅓ cups	355	21 9	153	7 4	0	22	20	2 2	0
Vegetables and fruits										
Tomatoes, cooked	½ cup	25	1 2	14	8	1,270	07	04	8	20
Green peppers, cooked	1 small	10	5	5	2	320	02	03	2	43
Corn, canned	½ cup	70	2 2	4	5	190	03	05	8	4
Squash, winter, yellow, boiled, mashed	½ cup	45	1 7	22	7	5,640	04	12	4	6
Bread and cereals										
Cornmeal, degermed, enriched	2 ounces	205	4 5	3	1 6	170	25	15	2 0	0
Bread, white, enriched	2 slices	125	4 0	36	8	0	12	08	1 0	0
Total		1 250	60 9	805	13 5	8,650	82	1 19	8 9	74

[1]Source of data B K Watt and A L Merrill, Composition of Foods—Raw, Processed Prepared U S Dept Agr, Agr Handb 8 1950

TABLE OF
FOOD COMPOSITION

TABLES OF FOOD COMPOSITION*

Constituents of 100 G of Edible Portion

Name	Proximate Composition							Minerals					Vitamins†					Average Portion		
	Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	A I U	B_1 mg	B_2 mg	Nicotinic Acid mg	C mg	Total Calories	Measure	Wt in g
DAIRY PRODUCTS																				
Cheese																				
Blue mold	368	40	21 5	30 5	6 0	2 0	0	315	339	5	700	92	1240	03	61	4	0	104	1 oz blue	28
Cheddar	398	37	25 0	32 2	3 7	2 1	0	725	495	1 0	1500	80	1400	02	43	Tr	0	113	1 oz (1" cube)	28
Cheddar processed	370	40	23 2	29 9	4 9	2 0	0	673	787	9	290	72	1300	02	41	Tr	0	105	1 oz cheddar	28
Cottage	95	76 6	19 5	5	1 5	2 0	0	96	189	3	250	74	20	02	31	1	0	27	1 oz cottage	28
Cream cheese	371	51	9 0	37 0	1 0	2 0	0	68	97	2	710	100	1450	01	22	1	0	106	1 oz	28
Swiss	370	39	27 5	28 0	3 8	1 7	0	925	563	9			1450	01	40	1	0	105	1 oz	28
Swiss processed	355	40	26 4	26 9	5 1	1 6	0	887	867	9			1390	01	40	1	0	101	1 oz	28
Cream light (sweet sour)	204	72 5	2 9	20 0	6	4 0	0	97	77	1	40	56	830	03	14	1	1	30	1 tbsp	15
Cream whipping	330	59	2 3	35 0	5	3 2	0	78	61	0	100	90	1440	02	11	1	1	50	1 tbsp	15
Ice cream plain	207	62 1	4 0	12 5	8	20 6	0	123	99	1			520	04	19	1	1	167	1 slice	81
Milk Cow																				
Fluid whole	68	87 0	3 5	3 9	7	4 9	0	118	93	1	50	140	160	04	17	1	1	166	1 cup	244
Fluid non fat	36	90 5	3 5	1	8	5 1	0	123	97	1	52	150	Tr	04	18	1	1	87	1 cup	246
Evaporated condensed	138	73 7	7 0	7 9	1 5	9 9	0	243	195	2	100	270	400	05	36	2	1	346	1 cup	252
Non fat solids dry	362	3 5	35 6	1 0	7 9	52 0	0	1300	1030	6	77	1130	40	35	1 96	1 1	7	28	1 tbsp	8
Malted beverage	104	78 2	4 6	4 4	1 0	11 8	0	135	123	3			2,0	07	21		1	281	1 cup	270
Chocolate flavored	74	83 0	3 2	2 2	8	10 6	0	109	91	1	4	33	90	03	16	1	1	185	1 cup	250
Milk, goat fluid	67	87 4	3 3	4 0	7	4 6	0	129	106	1	34	180	160	04	11	3	1	164	1 cup	244
Buttermilk	36	90 5	3 5	1	8	5 1	0	118	93	1	130	140	Tr	04	18	1	1	86	1 cup	244
Butter	716	15 5	6	81	2 5	4	0	20	16	0	980	23	3300	Tr	01	1	0	100	1 tbsp	14
Sherbert	123	68 1	1 5	0	4	30 0		50	40	0	174	218	0	02	08	Tr	0	118	½ cup	96

†For nutrients not mentioned in Tables see relevant chapters

FATS OILS AND SHORTENINGS

Butter	716	15 5	6	81	2 5	4	0	20	16	0	980	23	3300	Tr	01	1	0	100	1 tbsp	14
Fats cooking vegetable	884	0	0	100	0	0	0	0	0	0	4	0	0	0	0	0	0	1768	1 cup	200
Lard	902	0	0	100	0	0	0	0	0	0	3	2	0	0	0	0	0	126	1 tbsp	14
Margarine	720	15 5	6	81	2 5	4	0	20	16	0	1100	58	3300	0	0	0	0	100	1 tbsp	14
Mayonnaise	708	16	1 5	78	1 5	3 0	0	19	60	1 0	590	25	210	04	04	0	0	92	1 tbsp	13
Oils salad or cooking	884	0	0	100	0	0	0	0	0	0	2	1	0	0	0	0	0	124	1 tbsp	14
Salad dressing *French*	394	39 6	6	35 5	4 0	20 3	3	0	0	0			0	0	0	0	0	60	1 tbsp	15
Salt pork *fat*	783	8 0	3 9	85	3 5	0	0	Tr	Tr	6	1800	27	0	18	04	9	0	470	2 oz	60

FRUITS

Berries

Blackberries raw	57	84 8	1 2	1 0	5	12 5	4 2	32	32	9	2	150	200	04	04	4	21	82	1 cup	144
Blueberries raw	61	83 4	6	6	3	15 1	1 2	16	13	8	6	89	280	02	02	3	16	85	1 cup	140
Blueberries cnd sweet	98	73	4	4	2	26	1 0	41	6	5			40	01	01	2	13	245	1 cup	249
Cranberries raw	48	87 4	4	7	2	11 3	1 4	14	11	6	1	65	40	03	02	1	12	54	1 cup	113
Cranberry sauce cnd sweet	198	48 1	1	3	1	51 4	4	8	7	3	1	17	30	02	02	1	2	550	1 cup	277
Currants red raw	55	84 4	1 2	2	6	13 6	4 0	36	33	9	2	160	120	04			36	30	½ cup	55
Gooseberries	39	88 9	8	2	4	9 7	1 9	22	28	5	7	87	290				33	59	1 cup	150
Loganberries	62	82 9	1 0	6	5	15 0	1 4	35	19	1 2			200	03	07	3	24	90	1 cup	144
Raspberries black raw	74	80 6	1 5	1 6	6	15 7	6 8	40	37	9	3	190	0	02	07	3	24	100	1 cup	134
Raspberries red raw	57	84 1	1 2	4	5	13 8	4 7	40	37	9	5	130	130	02	07	3	24	70	1 cup	123
Raspberries red *frz*	98	74 3	7	2	2	24 7	2 1	12	17	6	7	97	80	02	07	5	21	84	3 oz	86
Strawberries raw	37	89 9	8	5	5	8 3	1 4	28	27	8	8	180	60	03	07	3	60	54	1 cup	149
Strawberries frozen	95	74 8	5	2	-	24 2	6	13	16	6	1 5	107	33	02	06	5	43	82	3 oz	86

Citrus Fruit

Grapefruit raw	40	88 8	5	2	4	10 1	3	22	18	2	5	200	Tr	04	02	2	40	77	1 cup sections	194
Grapefruit cnd sw	72	79 8	6	2	4	19 1	2	13	14	3			Tr	03	02	2	30	181	1 cup	249
Lemons	32	89 3	9	6	5	8 7	9	40	22	6	7	130	0	04	Tr	1	0	20	1 2 diam	100

* Reprinted from *Nutritional Data* second revised edition H J Heinz Company 1958 by courtesy of Dr Harold A Wooster Jr

* Signs and Symbols Used *Dashes* show that there is no value for a constituent reported in the literature although it seems reasonable to assume that it should be present

Trace (abbreviated Tr) is used to indicate values that would round *to zero* with the number of decimal places carried in these tables Zero means that for practical purposes there isn t enough of a constituent present to worry about

Tables of Food Composition (Continued)

Constituents of 100 G of Edible Portion

	Proximate Composition							Minerals					Vitamins					Average Portion		
Name	Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	A I U	B_1 mg	B_2 mg	Nicotinic Acid mg	C mg	Total Calories	Measure	Wt in g
FRUITS (Continued)																				
Limes	37	86 0	8	1	8	12 3	9	40	22	6	1	100	0	04	Tr	1	27	19	1 1¼" long	68
Oranges	45	87 2	9	2	5	11 2	6	33	23	4	3	170	190	08	03	2	49	70	1 med 3" diam	215
Tangerines	44	87 3	8	3	7	10 9	1 0	33	23	4	2	110	420	07	03	2	31	35	1 med 2½" diam	114
Melons																				
Cantaloupes	20	94 0	6	2	6	4 6	6	17	16	4	12	230	3420	05	04	5	33	37	½ melon 5" diam	385
Honey dew	32	90 5	5	0	5	8 5	4	17	16	4			40	05	03	2	23	49	1 2 × 7" wedge	150
Watermelon	28	92 1	5	2	3	6 9	6	7	12	2	3	110	590	05	05	2	6	45	½ sl ¾ × 10"	345
Tree Vine and other Fruits																				
Apples raw	58	84 1	3	4	3	14 9	1 0	6	10	3	2	74	90	04	03	2	5	76	1 med 2½ diam	150
Apples dry unckd	277	23 0	1 4	1 0	1 4	73 2	3 9	19	48	1 4			0	10	10	1 0	12	315	1 cup	114
Apricots raw	51	85 4	1 0	1	6	12 9	6	16	23	5	6	440	2790	03	05	8	7	54	3 apricots	114
Apricots cnd sw	80	77 3	6	1	6	21 4	4	10	15	3	2	65	1350	02	02	3	4	97	4 med ½s 2 tbsp	122
Apricots dry	262	24 0	5 2	4	3 5	66 9	3 2	86	119	4 9	11	1700	7430	01	16	3 3	12	393	40 ½s	150
Apricots frozen	97	73 7	7	1	1	24 9	6	9	119	9	5 4	228	2660	02	04	8	9	81	3 oz apricots	84
Avocado	245	65 4	1 7	26 4	1 4	5 1	1 8	10	38	6	3	340	290	06	13	1 1	16	280	½ 3½ × 3¼"	114
Bananas	88	74 8	1 2	2	8	23 0	6	8	28	6	5	420	430	04	05	7	10	88	1 med 6 × 1½"	150
Cherries all raw	61	83 0	1 1	5	6	14 8	3	18	20	4	1	260	620	05	06	4	8	94	1 cup pitted	154
Cherries red sour canned	48	86 6	8	3	4	11 9	1	11	12	3	3	55	720	03	02	2	6	122	1 cup pitted	254
Dates dried	284	20	2 2	6	1 8	75 4	2 4	72	60	2 1	1	790	60	09	10	2 2	0	505	1 cup pitted	177
Figs cnd sw	113	68 5	8	3	4	30 0	9	35	21	4	1	105	50	03	03	4	Tr	130	3 2 tbsp sirup	115
Figs dried	270	24	[illegible]	1 2	2 4	68 4	[illegible] 8	186	111	3 0	34	780	[illegible]	[illegible]	12	1 7	0	57	1 large 1 × 2	21

Grapes Raw																				
American (slip skin)	70	81 9	1 4	1 4	4	14 [illegible]						[illegible]	[illegible]	06	04	2	4	84	1 cup	153
European (adherent skin)	60	81 6	8	4	5	16 7		[illegible]	21	6	4	180	80	06	04	2	4	102	1 cup 10 grapes	160
Guavas raw	70	80 6	1 0	0	7	17 1	5 5	30	29	7			250	07	04	1 2	302	49	1 small	80
Peaches raw	46	80 9	5	1	5	12 0	6	8	22	0	5	160	980	02	05	9	8	45	1 med ~½ × 2" diam	114
Peaches cnd sw	68	80 9	4	1	4	18 2	4	5	14	4	5	31	450	01	02	7	4	175	1 cup peaches	258
Peaches frz sw	88	76 3	5	1	8	22 8	4	4	12	7	3	124	133	01	04	7	13	93	4 oz peaches	112
Peaches dry unckd	265	24 0	3 0	6	3 0	69 4	3 5	44	126	6 9	2	1100	3250	01	20	5 4	19	424	1 cup peaches	100
Pears raw	63	82 7	7	4	1	15 8	1 4	13	16	3	2	100	20	02	04	1	4	95	1 3 × 2½" diam	182
Pears cnd sw	68	81 1	2	1	2	18 4	8	8	10	2	8	52	Tr	01	02	1	2	50	2 ½s 2 tbsp sirup	117
Plums raw	50	85 7	7	2	5	12 9	5	17	20	5	6	170	3[illegible]0	06	04	5	5	30	1 2" diam	60
Plums cnd sw	76	78 6	4	1	5	20 4	3	8	12	1 1	18	110	230	03	03	4	1	186	1 cup plums	256
Prunes dry	268	24 0	2 3	6	2 1	71 0	1 6	54	85	3 9	6	600	1890	10	16	1 7	3	94	4 lg prunes	40
Raisins dry	268	24 0	2 3	5	2 0	71 2		78	129	3 3	21	720	[illegible]0	15	08	5	Tr	430	1 cup raisins	160
Rhubarb cnd sw	141	62 9	4	1	6	36 0	6	41	20	4	2	160	20	01		1	6	383	1 cup rhubarb	273
Rhubarb frz	74	80 2	6	2	6	19 2	9	99	14	8	6	212	83	02	06	2	7	202	1 cup rhubarb	273
FRUIT JUICES AND OTHER FRUIT PRODUCTS																				
Apple juice frozen or canned	50	85 9	1	0	3	13 8		6	10	5	4	100	40	02	03	Tr	1	124	1 cup	249
Apple sauce frz or cnd sw	72	79 8	2	1	2	19 7	6	4	8	4	3	55	30	02	01	Tr	1	185	1 cup	254
Apricot nectar	52	86 1	3	1	5	12 4	2	9	13	3 3	2 9	98	1090	Tr	01	Tr	1	170	1 cup	254
Fruit cocktail canned sweet	70	80 6	4	2	3	18 6	4	9	12	4	9	160	160	01	01	4	2	180	1 cup	257
Grape juice cnd sw	67	81 0	4	0	4	18 2		10	10	3	1	1[illegible]0		04	05	2	Tr	120	6 oz	180
Grapefruit juice canned sweet	52	85 3	5	1	4	13 7	1	8	11	3	4	150	Tr	03	02	2	35	131	1 cup	251
Lemon juice cnd	21	91 4	4	2	3	7 7	0	14	11	1			0	04	Tr	1	42	4	1 tbsp	15
Lime juice fresh	21	91 0	4	0	3	8 3	0	14	11	1	1 1	175	0	04	Tr	1	27	57	1 cup	246
Olives green	132	75 2	1 5	13 5	5 8	4 0	1 2	87	17	1 6	2400	55	300	Tr				72	10 mammoth	65
Olives ripe Mission	191	71 8	1 8	21 0	2 8	2 6	1 5	87	17	1 6	980	23	60	Tr	Tr			106	10 mammoth	65
Orange juice fresh	44	87 5	8	2	4	11 0	1	1[illegible]	16	2	3 6	82	190	08	03	2	49	108	1 cup	246
Orange juice cnd	44	87 5	8	2	4	11 1	1	10	18	3	[illegible]	190	100	07	02	2	42	135	1 cup	251
Orange and grapefruit juice cnd sw	52	85 1	5	1	4	13 9	1	9	15	3	4	170	40	05	02	2	38	132	1 cup	251
Pineapple juice cnd	49	86 2	3	1	4	13 0	1	15	8	5	5	140	80	0[illegible]	02	2	9	121	1 cup	249
Prune juice cnd	71	80 0	4	0	3	19 3		25	40	1 8	2	260		03	08	4	1	170	1 cup	210
Tangerine juice cnd	39	90 2	9	3	4	9 2		19	16	2	6	170	420	06	03	2	20	95	1 cup	246
Tomato juice cnd	21	93 [illegible]	1 0	2	1 0	4 3	2	7	15	4	230	230	10[illegible]0	05	03	8	16	[illegible]0	1 cup	242

Constituents of 100 G of Edible Portion

Name	Proximate Composition							Minerals					Vitamins					Average Portion		
	Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	A I U	B1 mg	B2 mg	Nicotinic Acid mg	C mg	Total Calories	Measure	Wt in g
GRAINS AND GRAIN PRODUCTS																				
Breakfast Cereals																				
Bran flakes	292	3 6	10 8	1 9	4 9	78 8	3 9	61	622	5 1	1400	1200	0	46	23	8 7	0	117	1 cup bran	40
Cork flakes*	385	3 6	8 1	4	2 9	85 0	6	11	58	2 2	660	160	0	41	10	2 2	0	96	1 cup	25
Farina ckd *	44	89 2	1 3	1	3	9 1	0	3	13	2	11	10	0	04	03	2	0	105	1 cup farina	238
Oat breakfast cereal*	396	4 0	14 5	7 0	4 3	70 2	2 0	160	350	4 1			0	82	19	1 9	0	100	1 cup oats	25
Oatmeal ckd	63	84 8	2 3	1 2	7	11 0	2	9	67	7	3	55	0	10	02	-	0	150	1 cup oatmeal	238
Puffed Rice*	392	3 5	5 9	6	2 3	87 7	5	21	116	1 8	9	100	0	46	08	5 5	0	55	1 cup	14
Puffed Wheat*	355	3 8	10 8	1 6	3 6	80 2	1 7	46	329	4 2	4	340	0	56	18	6 4	0	43	1 cup	12
ce flakes*	392	3 5	5 9	6	2 3	87 7	5	21	116	1 8	720	180	0	46	08	5 5	0	117	1 cup	30
heat flakes*	355	3 8	10 8	1 6	3 6	80 2	1 7	46	329	4 2	1300	320	0	56	18	6 4	0	125	1 cup	35
ıeat whole meal*	344	8 2	12 7	1 7	2 1	75 3	2 2	46	392	3 4	2	380	0	55	15	4 4	0	103	¼ cup wheat	30
RS MEALS AND OTHER FARINACEOUS MATERIALS																				
pearled light	349	11 1	8 2	1 0	9	78 8	5	16	189	2 0	3	160	0	12	08	3 1	0	710	1 cup barley	204
ıeat flour light	348	12	6 4	1 2	9	79 5	5	11	88	1 0			0	08	04	4	0	342	1 cup	98
rits * ckd	51	87 1	1 2	1	6	11 0	1	1	10	3			40	04	03	4	0	122	1 cup grits	242
n meal whole	362	12	9 0	3 4	1 1	74 5	1 0	6	178	1 8			440	30	08	1 9	0	459	1 cup meal	127
ı meal degermed*	363	12	7 9	1 2	5	78 4	6	6	99	2 3	7	120	300	44	26	3 5	0	527	1 cup meal	145
*	370	10 5	10 9	8	4	77 4	4	28	112	1 3	2	86	0	37	26	1 3	0	625	1 cup farina	169
rye dark	318	11	16 3	2 6	2 0	68 1	2 4	54	536	4 5	1	860	0	61	22	2 7	0	285	1 cup rye	80
wheat 80% extn	365	12	12 0	1 3	7	74 1	5	24	191	1 3	1	120	0	26	07	2 0	0	400	1 cup stirred	110
wheat self rising*	350	12	9 2	1 0	4 0	73 8	4	272	484	2 9	1,000	90	0	44	28	3 5	0	384	1 cup stirred	110
ır wheat all purpose*	364	12	10 5	1 0	4	76 1	3	16	87	2 9	1	86	0	44	26	3 5	0	400	1 cup stirred	110
our wheat cake	364	12	7 5	8	3	79 4	2	17	73	5			0	03	03	7	0	364	1 cup stirred	100
Rice brown	360	12	7 5	1 7	1 1	77 7	6	39	303	2 0	9	150	0	32	05	4 6	0	748	1 cup rice	208
Rice converted	362	12	7 6	3	4	79 4	2	24	136	8	4	170	0	20	03	3 8	0	677	1 cup rice	187

Rice white	362	12 3	7 6	3	4	79 4	2	24	136	8	2	130	0	07	03	1 6	0	692	1 cup rice	191
Starch pure	362	12	5	2	3	87	1	0	0	0	4	4	0	0	0	0	0	29	1 tb p starch	8
Tapioca dry	360	12 6	6	‐	2	86 4	1	12	12	1 0	5	19	0	0	0	0	0	547	1 cup tapioca	152
Wild rice	364	8 5	14 1	7	1 4	75 3	1 0	19	339		7	220	0	45	63	6 2	0	593	1 cup rice	163
Wheat germ	361	11 0	25 2	10 0	4 3	49 5	2 5	84	1096	8 1	2	780	0	2 05	80	4 6	0	246	1 cup germ	68
BAKED AND COOKED PRODUCTS																				
Breads																				
Boston brown*	219	44 5	4 8	2 1	2 6	46 0	3	185	158	2 9	280	360	140	13	17	1 9	0	105	1 ¾ slice	48
Cracked wheat*	259	36 0	8 5	2 2	1 9	51 4	5	83	126	2 0	620	250	0	25	19	2 5	0	60	1 ½ slice	23
French or Vienna*	270	35 5	8 1	2 7	1 7	52 0	2	24	71	1 8			0	24	15	2 2	0	1225	1 pound	453
Raisin*	284	30 2	7 1	3 1	1 8	57 8	2	80	104	1 8			10	24	15	2 2	0	65	1 ½" slice	23
Rye (⅓ rye flour)	244	35 3	9 1	1 2	2 0	52 4	4	72	147	1 6	590	160	0	18	08	1 5	0	57	1 ½ slice	23
White 4% non fat milk solids*	275	34 7	8 5	3 2	1 8	51 8	2	79	92	1 8	640	180	0	24	15	2 2	0	63	1 ½" slice	23
Whole wheat	240	36 6	9 3	2 6	2 5	49 0	1 5	96	263	2 2	930	230	0	30	13	3 0	0	55	1 ½" slice	23
Bread crumbs dry	385	8 5	11 9	4 5	2 6	72 5	2	111	129	2 6			0	27	22	3 1	0	339	1 cup crumbs	88
Cakes																				
Angel food	270	31 6	8 4	3	1 0	58 7	0	6	24	3			0	01	14	2	0	110	2 sec of 8 cake	41
Foundation	350	25 1	5 9	11 7	1 4	55 9	1	126	120	5			160	03	08	2	0	230	1 sq 3 × 2 × 1¾"	66
Fruit dark	354	22 9	5 2	13 8	2 2	55 9	1 2	97	126	2 8			160	14	14	1 1	0	106	2 × 2 × ½	30
Plain	327	26 8	6 4	8 2	1 6	57 0	1	155	137	4			120	03	08	3	0	161	1 2¾ cupcake	50
Sponge	291	31 8	7 9	5 0	9	54 4		28	110	1 4			520	05	15	2	0	117	2 sec of 8 cake	40
Corn bread*	219	49 2	6 7	4 7	2 8	36 6	2	139	155	1 9			130	17	23	1 3	0	103	1 2¾ muffin	48
Crackers Graham	393	5 5	8 0	10 0	2 2	74 3	8	20	203	1 9	710	330	0	30	12	1 5	0	55	2 medium	14
Crackers Saltines	431	4 6	9 2	11 8	3 3	71 1	4	19	92	1 0	1100	120	0	06	04	1 0	0	34	2 2 square	8
Custard baked	114	77 3	5 3	5 4	8	11 2	0	114	119	5			340	05	20	1	Tr	283	1 custard cup	248
Doughnuts	425	18 7	6 6	21 0	1 0	52 7	2	73	286	7			140	16	13	1 2	0	136	1 doughnut	32
Fig bars	350	13 8	4 2	4 8	1 4	75 8	1 7	63	69	1 3			0	02	06	9	0	87	1 fig large bar	25
Gingerbread	327	30 4	3 9	12 0	2 1	51 6	1	114	71	2 5			100	04	08	1 0	0	180	1 2 cube	55
Macaroni* dry	377	8 6	12 8	1 4	7	76 5	4	22	165	2 9	1	160	0	88	37	6 0	0	463	1 cup dr	123
Macaroni and cheese ckd	211	58 1	8 1	11 0	3 1	19 7	1	191	169	5			450	03	16	4	Tr	464	1 cup	220
Muffins*	280	37 4	8 0	8 4	2 2	42 1	1	206	191	1 6			100	18	21	1 5	0	135	1 2¼ muffin	48
Noodles (egg) ckd	67	83 8	2 2	6	6	12 8	1	4	35	5			30	14	06	1 0	0	107	1 cup	60
Pancakes wheat*	218	55 4	6 8	9 2	2 0	26 6	1	158	154	1 3			200	18	21	1 3	Tr	60	1 4 diam	27
Pancakes buckwheat	176	62 0	6 1	8 4	2 6	20 9	5	249	302	1 2			110	16	16	9	Tr	48	1 4 diam	27

* Enriched fortified or restored to legal standard when one exists

Constituents of 100 G of Edible Portion

Name	*Proximate Composition* Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	*Minerals* Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	*Vitamins* A I U	B_1 mg	B_2 mg	Nicotinic Acid mg	C mg	*Average Portion* Total Calories	Measure	Wt in g
BAKED AND COOKED PRODUCTS (*Continued*)																				
Pies																				
Apple	246	47 8	2 1	9 5	1 1	39 5	7	7	24	4			160	03	02	2	1	330	1 4 sector of	220
Mince	252	43 0	2 5	6 9	2 0	45 6	5	16	40	2 2			10	07	04	4	1	340	9" diameter	135
Pumpkin	202	58 9	4 2	9 6	1 5	25 8	6	54	81	8			1910	03	12	3	0	265	pie	131
Pretzels	369	8 0	8 8	3 2	5 5	74 5	3	12	71	7	1700	130	0	01	04	7	0	18	5 small sticks	5
Rolls plain*	309	28 5	9 0	5 5	1 9	55 1	2	55	96	1 8			0	24	15	2 2	0	120	1 roll (1/12 lb)	39
Rolls sweet	323	28 4	8 5	7 8	1 5	53 8	2	63	104	1 8			0	24	15	2 2	0	178	1 roll	55
Rye wafers	324	6 5	12 4	1 2	4 6	75 3	2 1	50	400	4 4	1500	600	0	32	20	1 2	0	43	2 wafers	13
Spaghetti* cooked	149	60 6	5 1	6	3 5	30 2	2	9	65	1 1			0	17	10	1 4	0	220	1 cup	148
Waffles*	287	40	9 3	10 6	2 3	37 8	1	192	204	1 8			360	18	27	1 3	0	216	1 4½ × 5⅝ × ½"	75
NUTS AND NUT PRODUCTS																				
Almonds dry	597	4 7	18 6	54 1	3 0	19 6	2 7	254	475	4 4	160†	710†	0	25	67	4 6	Tr	850	1 cup almonds	140
Brazil nuts shelled	646	5 3	14 4	65 9	3 4	11 0	2 1	186	693	3 4	1	670	Tr	86				905	1 cup Brazils	140
Cashews roasted	578	3 6	18 5	48 2	2 7	27 0	1 3	46	428	5 0	200†	560†		63	19	2 1		810	1 cup cashews	140
Chestnuts fresh	191	53 2	2 8	1 5	1 0	41 5	1 1	48	48	4 1	2	410	0	08	24	1 0	0	95	20 chestnuts	50
Cocoanut dry sw	556	3 3	3 6	39 1	8	53 2	4 1	43	191	3 6	16	770	0	Tr	Tr	Tr	0	344	1 cup shreds	62
Peanuts roasted	559	2 6	26 9	44 2	2 7	23 6	2 4	74	393	1 9	460†	700†	0	30	13	16 2	0	805	1 cup	144
Peanut butter	576	1 7	26 1	47 8	3 4	21 0	2 0	74	393	1 9	120	820	0	12	13	16 2	0	92	1 tbsp	16
Pecans raw	696	3 0	9 4	73 0	1 6	13 0	2 2	74	324	2 4	3	420	50	72	11	9	2	752	1 cup of ½ s	108
Walnuts Eng raw	654	3 3	15 0	64 4	1 7	15 6	2 1	83	380	2 1	2	450	30	48	13	1 2	3	654	1 cup ½ s	100
MEAT POULTRY AND SEA FOOD																				
Beef																				
Chuck ckd	309	51	26	22	7	0	0	11	117	3 1	51	360	0	05	20	4 1	0	265	3 oz chuck	86
Hamburger ckd	364	47	22	30	1 1	0	0	9	158	2 8			0	08	19	4 8	0	316	3 oz ground	86

Porterhouse ckd	312	49	~3	~7	1 1	0	0	11	170	3 0			0	06	18	4 7	0	293	3 oz steak	86
Rib roast ckd	319	51	24	21	1 2	0	0	10	185	3 0			0	06	18	4 3	0	266	3 oz roast	86
Round ckd	233	59	27	13	1 3	0	0	11	224	3 4			0	08	23	~ 5	0	197	3 oz round	86
Corn beef cnd	216	59 3	25 3	12	3 4	0	0	20	106	4 3	1300	60	0	02	24	3 4	0	180	3 oz corned	86
Corn beef hash cnd	141	70 4	13 7	6 1	2 6	7 2	2	26	146	1 3			Tr	03	14	2 9	0	120	3 oz hash	86
Dried or chipped beef	203	47 7	34 3	6 3	11 6	0	0	20	404	5 1	4300	200	0	07	32	3 8	0	11~	2 oz dried	56
Roast beef cnd	~24	60	25	13	2	0	0	16	116	2 4			0	02	23	4 2	0	189	3 oz roast	86
Lamb																				
Med fat raw	317	55 8	1~ 7	27 7	8	0	0	9	157	2 4			0	14	20	4 5	0	273	3 oz	86
Rib chop raw	356	51 9	14 9	32 4	8	0	0	9	138	2 2	98	340	0	13	18	4 3	0	409	4 oz chop	115
Rib chop ckd	418	40	24	35	1 2	0	0	11	200	3 0			0	14	26	~ 6	0	480	4 oz chop	115
Leg roast raw	235	63 7	18 0	17 5	9	0	0	10	213	2 7	78	380	0	16	22	~ 2	0	202	3 oz roast	86
Leg roast ckd	274	~6	24	19	1 1	0	0	10	257	3 1			0	14	25	5 1	0	314	3 oz roa t	86
Pork																				
Bacon fried	607	13	25	55	6	1	0	25	255	3 3	2400	390	0	48	31	4 8	0	97	2 sl bacon	16
Bacon Canadian raw	231	56	2~ 1	15	6 2	3	0	13	210	3 3			0	91	25	~ 2	0	26~	4 oz bacon	115
Ham fresh raw	344	53	1~ 2	31	8	0	0	9	168	2 3			0	74	18	4 0	0	296	3 oz ham	86
Ham cured ckd	397	39	23	33	5 4	4	0	10	166	2 9	1100	340	0	54	21	4 2	0	340	3 oz ham	86
Pork luncheon meat cnd	289	55 2	14 9	24 3	4 1	1 5	2	9	161	2 2			0	32	22	2 8	0	16~	2 oz	57
Veal																				
Veal med fat	190	68	19 1	12	1 0	0	0	11	193	2 9	48	330	0	14	25	6 4	0	219	4 oz	115
Veal cutlet ckd	219	60	28	11	1 4	0	0	12	258	3 5			0	08	~8	6 1	0	184	3 oz cutlet	86
Stew meat ckd	296	53	2~	21	8	0	0	11	124	3 0			0	05	24	4 6	0	252	3 oz	86
VARIETY MEATS AND MIXTURES																				
Brains	125	78 9	10 4	8 6	1 4	8	0	16	330	3 6	1~0	340	0	23	26	4 4	18	106	3 oz brains	86
Chile con carne	200	66 9	10 3	14 8	~ 2	5 8	2	38	152	1 4			150	02	12	2 2		170	½ cup	85
Heart beef raw	108	77 6	16 9	3 7	1 1	7	0	9	203	4 6	90	160	30	58	89	7 8	6	9~	3 oz heart	86
Kidneys beef raw	141	74 9	1~ 0	8 1	1 1	9	0	9	~~1	7 9	210	310	11~0	37	2 55	6 4	13	120	3 oz kidneys	86
Liver beef raw	136	69 7	19 7	3 2	1 4	6 0	0	7	358	6 6	110	380	43900	26	3 33	13 7	31	117	3 oz liver	86
Liver beef fried	208	57 2	23 6	7 7	1 8	9 7	0	8	486	7 8			53500	26	3 96	14 8	31	118	2 oz liver	57
Liver calf raw	141	70 8	19 0	4 9	1 3	4 0	0	6	343	10 6	110	380	22500	21	3 12	16 1	36	121	3 oz liver	86
Liver pork raw	134	72 3	19 7	4 8	1 5	1 7	0	10	362	18 0	77	350	14200	40	2 98	16 7	23	11~	3 oz liver	86

* Enriched fortified or restored to legal standard when one exists † When roasted and salted

TABLES OF FOOD COMPOSITION (Continued)

Constituents of 100 G of Edible Portion

Name	Proximate Composition							Minerals					Vitamins					Average Portion		
	Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	A I U	B1 mg	B2 mg	Nicotinic Acid mg	C mg	Total Calories	Measure	Wt in g
VARIETY MEATS AND MIXTURES (Continued)																				
Sausage bologna	221	62 4	14 8	15 9	3 3	3 6		9	112	2 2	1300	230	0	18	19	2 7	0	467	1 × 1½" diam	211
Sausage frankfurter cooked	248	62	14	20	2	2		6	49	1 2	1100	220	0	16	18	2 5	0	124	1 7 × ¾"	51
Sausage liverwurst	263	59 0	16 7	20 6	2 2	1 5		9	238	5 4	892	149	5750	17	1 12	4 6	0	150	2 oz liverwurst	57
Sausage pork raw	450	41 9	10 8	44 8	2 1	0	0	6	100	1 6	740	140	0	43	17	2 3	0	158	2 3½" long	35
Tongue beef	207	68	16 4	15	9	4	0	9	187	2 8	100	260	0	12	29	5 0	0	235	4 oz tongue	115
FISH AND SHELL FISH																				
Bluefish baked	155	69 2	27 4	4 2	1 9	0	0	23	293	7				12	11	2 2		178	4 oz bluefish	115
Clams raw	81	80 3	12 8	1 4	2 1	3 4	0	96	139	7 0	180	210	110	10	18	1 6		92	4 oz clams	115
Cod raw	74	82 6	16 5	4	1 2	0	0	10	194	4	60	360	0	06	09	2 2	2	85	4 oz cod	115
Cod dried	375	12 3	81 8	2 8	7 0	0	0	50	891	3 6	8100	160	0	08	45	10 9	0	106	1 oz dry cod	28
Crabs cnd or ckd	104	77 2	16 9	2 9	1 7	1 3	0	45	182	9	1000	110		05	06	2 5		90	3 oz crabs	86
Flounder raw	68	82 7	14 9	5	1 3	0	0	61	195	8				06	05	1 7		78	4 oz flounder	115
Frog legs raw	73	81 9	16 4	3	1 1	0	0	18	147	1 1			0	14	25	1 2		82	4 oz frog legs	115
Haddock ckd	158	66 9	18 7	5 5	1 9	7 0	0	18	182	6				04	09	2 6		158	1 fillet 4 × 3 × ½"	100
Halibut raw	126	75 4	18 6	5 2	1 0	0	0	13	211	7	56	540	440	07	06	9 2		145	4 oz halibut	115
Halibut ckd	182	64 2	26 2	7 8	1 9	0	0	14	267	8				06	07	10 5		230	1 fillet 4 × 3 × ½"	126
Herring raw	191	67 2	18 3	12 5	2 7	0	0	10	256	1 1			110	02	15	3 4		191	1 small herring	100
Herring kippered	211	61 0	22 2	12 9	4 0	0	0	66	254	1 4			0	Tr	28	2 9		211	1 small herring	100
Lobster raw	88	79 2	16 2	1 9	2 2	5	0	61	184	6	210	180		13	06	1 9		89	¼ average	100
Lobster cnd	92	77 2	18 4	1 3	2 7	4	0	65	192	8				03	07	2 2		78	3 oz	86
Mackerel cnd	182	66 0	19 3	11 1	3 2	0	0	185	274	2 1			430	06	21	5 8		155	3 oz	86
Oysters raw	84	80 5	9 8	2 1	2 0	5 6	0	94	143	5 6	73	110	320	15	20	1 2		200	13–19 med 1 cup	238
Oyster stew	91	82 6	5 3	5 4	1 4	5 3	0	117	110	1 5			280	06	18	4		244	1 cup 6–8 oysters	240
Salmon raw	223	63 4	17 4	16 5	1 0	[illegible]			289	9	48	410	310	10	23	7 2	9	192	3 oz salmon	86

Salmon cnd	203 64 7 19 7	13 ~ 2 4	0	0	154 289 9	540	300	230	03	14 7 3	0 120	3 oz salmon	86
Sardines cnd	211 57 4 25 7	11 0 4 ~	1 2	0	386 586 2 7	510	560	220	02	17 4 8	0 182	3 oz drained	86
Pilchard cnd	200 65 2 17 7	13 5 2 9	7	0	381 168 4 1	760	260	30	01	30 7 4	0 171	3 oz pilchards	86
Scallops raw	78 80 3 14 8	1 1 4	3 4	0	26 208 1 8	150	420	0	04	10 1 4	90	4 oz scallops	115
Shad raw	168 70 2 18 7	9 8 1 4	0	0	260 5				15	24 8 4	191	4 oz shad	115
Shrimp cnd	127 66 2 26 8	1 4 5 8		0	115 -63 3 1	140	220	60	01	03 2 2	0 110	3 oz shrimp	86
Swordfish ckd	178 64 8 27 4	6 8 1 7	0	0	20 251 1 1			2300	05	06 10 3	0 223	1 steak 3 × 3 × ½	125
Tuna fish cnd	198 60 0 23 0	8 2 2 7	0	0	8 351 1 4	800	240	80	05	12 12 8	0 170	3 oz drained solids	86
EGGS AND POULTRY													
Chicken fryers raw	112 74 5 20 5	2 7 1 1	0	0	15 188 1 8	78	320	0	10	24 5 6	0 210	1 breast	224
Chicken roasters raw	200 66 0 20 2	12 6 1 0	0	0	14 200 1 5	110	250	0	08	16 8 0	0 227	4 oz chicken	115
Chicken cnd	199 61 9 29 8	8 0 2 4	0	0	14 148 1 8			0	04	16 6 4	0 169	3 oz chicken	86
Chicken liver	141 69 6 22 1	4 0 1 7	2 6	0	16 240 7 4	51	160	32200	20 2	46 11 8	20 106	2 med livers	75
Duck	322 54 3 16 1	28 6 1 0	0		9 172 2 4				12	40 7 9	8 370	4 oz duck	115
Goose	366 49 7 15 9	33 6 9	0	0	9 176 2 4				14		13 420	4 oz goose	115
Turkey	268 58 3 20 1	20 2 1 0	0	0	23 320 3 8	40-92 310	320	Tr	09	14 8 0	0 304	4 oz turkey	115
Eggs Raw													
White	50 87 8 10 8	0 6	8	0	6 17 2	110	100	0	0	26 1 0	15	1 white	31
Yolk	361 49 4 16 3	31 9 1 7	7	0	147 586 7 2	26	100	3210	27	35 Tr 0	61	1 yolk	17
Whole	162 74 0 12 8	11 5 1 0	7	0	54 210 2 7	81	100	1140	10	29 1 0	77	1 medium egg	54
Eggs Dried													
White	398 3	85 9 0	4 9 6 3	0	49 135 1 6			0	0 2 05	7 0	223	1 cup whites	56
Yolk	693 3	31 2 61 2	3 3 1 3	0	282 1123 13 8			5540	50 66	1 0	666	1 cup yolks	96
Whole	592 5	16 8 42 0	3 6 2 5	0	190 767 8 8			3740	34 1 06	2 0	640	1 cup	108
SUGARS AND SWEETS													
Candied Peel													
Citron	314 18 0	2 3 1 3 80 2	1 4	83	24 8 290	120				89	89	1 oz citron	28
Ginger root	340 12	3 2 4 87 1	7								85	1 small piece	25
Lemon orange or grapefruit	316 17 4	4 3 1 3 80 6	2 3		50	12					32	1 small piece	10
Butterscotch	410 5 0 0	8 9 5 85 6	0	20	7 1 8		0	0 Tr	Tr	0	20	¼ sq × ¼	5
Caramels	415 7 0 2 9	11 6 1 77 5	0	126	90 2 3		170	02 14	1 Tr		42	¼ sq × ½	10
Chocolate swtnd milk	503 1 1 6	33 5 1 7 55 7	5	216	283 4 0 86	420	150	10 38	8	0	30	¼ × 1¼ × ¼	6
Same with almonds	532 6 8	38 6 1 8 50 0	6	208	249 2 9		140	13 51	1 1	0	32	Same	6

TABLES OF FOOD COMPOSITION (*Continued*)

Constituents of 100 G. of Edible Portion

Name	*Proximate Composition*							*Minerals*					*Vitamins*					*Average Portion*		
	Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	A I.U.	B_1 mg	B_2 mg	Nicotinic Acid mg	C mg	Total Calories	Measure	Wt. in g
SUGARS AND SWEETS (*Continued*)																				
Chocolate creams	394	9	4	14	1	72					10	110					0	55	1¼" diam × ¼"	14
Fondant	362	8	0	0	1	91	0	0	0	0			0	0	0	0	0	28	1" sq × ¾"	8
Fudge plain	411	5	1.7	11.3	.7	81.3	.3	48	67	.3			220	.01	.07	.1	Tr	185	2 sq × ¾"	45
Hard candy	383	1	0	0	0	99	0	0	0	0			0	0	0	0	0	31	3 ¾ diam	8
Marshmallows	325	15	3	0	1	81		0	0	0	41	6	0	0	0	0	0	98	5 1¼" diam	30
Peanut brittle	441	2	8.3	15.5	1.3	72.8	.8	39	124	2.0			30	.09	.05	4.9	0	66	1½ × 3	15
Chocolate bitter	501	2.3	5.5	52.9	3.2	29.2	2.6	98	446	4.4	4	830	60	.05	.24	1.1	0	30	¾" × 1½" × ½"	6
Chocolate plain sw	471	1.1	2	29.8	1.4	62.7	1.4	63	287	2.8	35	230	30	.03	.15	.6	0	28	Same	6
Chocolate sirup	209	39.0	1.2	1.1	.6	58.6	.6	15	86	1.4	60	130						40	1 tbsp syrup	19
Cocoa breakfast	293	3.9	8	23.8	5.0	48.9	4.6	125	712	11.6	57	3200	30	.12	.38	2.3	0	15	2 tsp cocoa	5
Cocoa beverage all milk	95	79.0	3.8	4.6	.9	10.9	.1	110	114	.4			160	.04	.19	.2	1	230	1 cup cocoa	240
Honey	294	20	.3	0	.2	79.5		5	16	.9	7	10	0	Tr	.04	.2	4	62	1 tb p honey	21
Jams marmalades etc	278	28	.5	.3	.4	70.8	.6	12	12	.3	7–13	9–78	10	.02	.02	.2	6	55	1 tbsp jam	20
Jellies	252	34.5	.2	0	.3	65.0	0	13	12	.3			10	.02	.02	.2	4	50	1 tbsp jelly	20
Molasses cane light	252	24			6.3	65		165	45	4.3	80	1500		.07	.06	.2		50	1 tbsp molasses	20
Molasses cane blackstrap	213	24			.5	55		579	85	11.3				.28	.25	2.1		43	1 tbsp molasses	20
Syrup table blends	286	25	0	0	.6	74		46	16	4.1	68	4	0	0	.01	.1	0	57	1 tbsp sirup	20
Sugars cane or beet	385	.5	0	0	0	99.5	0				3	0.5						48	1 tbsp sugar	12
Sugar brown	370	3	0	0	1.2	95.5		76	37	2.6	24	230	0	0	0	0	0	51	1 tbsp sugar	14
Corn sugar	348	7.5			.3	90					1	0.4	0	0	0	0	0	45	1 tbsp sugar	13
Maple sugar	349	7.[illegible]			.9	90												104	Piece 1¾ × 1¼ × ½"	30
VEGETABLES																				
Roots and Tubers																				
Beet red raw	42	87.6	1.6	.1	1.1	9.6	.9	27	43	1.0	110	350	20	.02	.05	.4	10	58	1 cup diced	134
Same cooked	41	88.3	1.0	.1	.8	9.8	.8	21	31	.7			20	.02	.04	.3	7	68	1 cup ckd diced	165

Same canned	34	90 3	9	1	8	7 9	5	15	29	6	36	120	20	01	02	1	5	82	Canned 1 cup	246
Carrots raw	42	88 2	1 2	3	1 0	9 3	1 1	39	37	8	31	410	12000	06	06	5	4	45	Grated 1 cup	110
Carrots canned	30	91 5	6	5	1 0	6 4	8	26	26	6	280	110	17500	02	02	3	3	44	Diced 1 cup	145
Parsnip raw	78	78 6	1 5	5	1 2	18 2	2 2	57	80	7	7	740	0	08	12	2	18	94	¾ cup diced	120
Parsnips cooked	60	83 5	1 0	5	1 1	13 9	2 1	57	80	7			0	06	10	2	12	94	Diced 1 cup	155
Potatoes sweet raw	123	68 5	1 8	7	1 1	27 9	1 0	30	49	7	4	530	7700	09	05	6	22	185	1 6 × 1²	150
Same boiled	123	68 5	1 8	7	1 1	27 9	1 0	30	49	7			7700	09	05	6	20	252	Boiled 1 5 × 2 5″	205
Same candied	179	57 4	1 5	3 6	1 3	36 2	8	36	45	9			6250	04	04	5	9	270	1 6 × 1¼ candied	150
Potatoes white raw	83	77 8	2 0	1	1 0	19 1	4	11	56	7	8	410	20	11	04	1 2	17	83	1 med 2½ diam	100
Same baked	98	73 8	2 4	1	1 2	22 5	5	13	66	8			20	11	05	1 4	17	97	1 med 2½ diam	100
Same boiled	83	77 8	2 0	1	1 0	19 1	4	11	56	7			20	10	04	1 2	15	120	1 med potato	142
Radishes raw	20	93 6	1 2	1	1 0	4 2	7	37	31	1 0	9	260	30	03	02	3	24	4	4 small radishes	40
Rutabagas raw	38	89 1	1 1	1	8	8 9	1 3	55	41	4	5	260	330	07	08	9	36	45	Diced ⅔ cup	120
Rutabagas cooked	32	90 8	8	1	8	7 5	1 4	55	41	4			350	05	07	7	21	50	Ckd diced 1 cup	155
Turnips raw	32	90 9	1 1	2	7	7 1	1 1	40	34	5	37	230	Tr	05	07	5	28	43	1 cup diced	134
Turnips cooked	27	92 3	8	2	7	6 0	1 2	40	34	5			Tr	04	06	4	18	42	1 cup diced	155
LEAF AND STEM VEGETABLES																				
Asparagus raw	21	93 0	2 2	2	7	3 9	7	21	62	9	2	240	1000	16	19	1 4	33	16	6 6 stalks	75
Asparagus ckd	20	92 5	2 4	2	1 3	3 6	8	19	53	1 0			1040	13	17	1 2	23	36	1 cup cut spears	175
Asparagus cnd	18	93 6	1 9	3	1 3	2 9	5	18	43	1 7	410	130	600	07	10	9	15	22	6 med spears	126
Asparagus frz	21	92 6	3 2	2	6	3 3	8	22	66	1 3	3	239	880	17	15	1 2	23	23	6 med spears	110
Beet greens raw	27	90 4	2 0	3	1 7	5 6	1 4	118	45	3 2	130	570	6700	08	18	4	34	27	1 cup beet greens	100
Beet greens ckd	27	90 4	2 0	3	1 7	5 6	1 4	118	45	3 2			7440	05	16	4	15	39	1 cup beet greens	145
Brussels sprouts raw	47	84 9	4 4	5	1 3	8 9	1 3	34	78	1 3	11	450	400	08	16	7	94	47	1 cup sprouts	100
Brussels sprouts ckd	47	84 9	4 4	5	1 3	8 9	1 3	34	78	1 3			400	04	12	5	47	60	1 cup cooked	130
Brussels sprouts frz	36	88 4	3 3	2	9	7 3	1 3	31	64	1 2	11	300	540	10	12	6	83	36	1 cup sprouts	100
Cabbage raw	24	92 4	1 4	2	8	5 3	1 0	46	31	5	5	230	80	06	05	3	50	24	Shredded 1 cup	100
Cabbage ckd	24	92 4	1 4	2	8	5 3	1 0	46	31	5			90	05	05	3	31	40	Ckd diced 1 cup	170
Sauerkraut cnd	22	91 2	1 4	3	2 7	4 4	9	36	18	5	630	140	40	03	06	1	16	32	Cnd drained 1 cup	150
Celery raw	18	93 7	1 3	2	1 1	3 7	7	50	40	5	110	300	0	05	04	4	7	18	Raw diced 1 cup	100
Chard leaves raw	27	91 0	2 6	4	1 2	4 8	8	105	36	2 5	84	380	8720	06	18	4	38	27	Leaves 1½ cups	100
Chard leaves and stalks ckd	21	91 8	1 4	2	2 2	4 4	9	105	36	2 5			3110	04	06	4	17	30	1 cup chard	145
Chicory French endive	21	94 2	1 6	3	1 0	2 9	8	18	21	7			10000	05	20		15	3	¼ sm head	15
Chives	52	86 0	3 8	6	1 8	7 8	2 0	48	57	8 4			500	12			70	4	1 tbsp chopped	7
Cress water	18	93 6	1 7	3	1 1	3 3	5	195	46	2 0			4720	08	16	8	77	5	⅓ cup water cress	20
Dandelion greens ckd	44	85 8	2 7	7	2 0	8 8	1 8	187	70	3 1	76	430	15170	13	12	7	16	80	1 cup greens ckd	180
Endive raw	20	93 3	1 6	2	9	4 0	8	79	56	1 7	18	400	3000	07	12	4	11	90	1 lb raw	460

TABLES OF FOOD COMPOSITION (*Continued*)

Constituents of 100 G of Edible Portion

Name	Proximate Composition: Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	Minerals: Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	Vitamins: A I U	B_1 mg	B_2 mg	Nicotinic Acid mg	C mg	Average Portion: Total Calories	Measure	Wt g
LEAF AND STEM VEGETABLES (*Continued*)																				
Kale raw	10	86 6	3 9	6	1 7	7 2	1 2	225	62	2 2	110	410	7540	10	26	2 0	115	70	1¼ cup kale	175
Kale ckd	10	86 6	3 9	6	1 7	7 2	1 2	225	62	2 2			8380	07	23	1 7	51	45	1 cup ckd kale	110
Kohlrabi raw	30	90 1	2 1	1	1 0	6 7	1 1	46	50	6			Tr	06	05	2	61	41	1 cup kohlrabi	138
Lettuce headed	15	94 8	1 2	2	9	2 9	6	22	25	5	12	140	540	04	08	2	8	7	2 lg or 4 sm leaves	50
Mustard greens ckd	22	92 2	2 3	3	1 2	4 0	8	220	38	2 9	48	450	7180	06	18	7	45	31	1 cup greens	140
Onions mature raw	45	87 5	1 4	2	6	10 3	1	32	44	5	1	130	50	03	04	2	9	50	1 2½" diam	110
Onions mature ckd	38	89 5	1 0	2	6	8 7	8	32	44	5			50	02	03	2	6	79	1 cup onions	210
Onions young green	45	87 6	1 0	2	6	10 6	1 8	135	24	9			50	03	04	2	24	23	6 small less tops	50
Parsley	50	83 9	3 7	1 0	2 4	9 0	1 8	193	84	4 3	28	880	8230	11	28	1 4	193	1	1 tbsp parsley	3 5
Spinach raw	20	92 7	2 3	3	1 5	3 2	6	81	55	3 0	82	780	9420	11	20	6	59	22	Raw 4 oz	115
Spinach ckd	26	90 8	3 1	6	1 9	3 6	1 0	124	33	2 0			11780	08	20	6	30	46	Cooked 1 cup	80
Spinach cnd	20	92 3	2 3	4	1 8	3 0	7	90	33	1 6	320	260	6790	02	10	3	14	45	Canned 1 cup	232
Spinach frz	23	91 7	3 4	4	1 2	3 5	8	120	44	3 1	62	365	8700	09	15	5	24	17	Frz 1¼ cup	50
Turnip greens raw	30	89 5	2 9	4	1 8	5 4	1 2	259	50	2 4	10	440	9540	09	46	8	136	15	Raw ¾ cup	50
Turnip greens ckd	30	89 5	2 9	4	1 8	5 4	1 2	259	50	2 4			10600	06	41	7	60	43	Cooked 1 cup	145
FLOWER FRUIT AND SEED VEGETABLES																				
Artichoke	63	83	2 9	4	1 1	11 9	3 2	47	94	1 9	43	430	390	15	03		11	33	1 3 diam	50
Beans																				
Red kidney raw	336	12 2	23 1	1 7	3 6	59 4	3 5	163	437	6 9			0	57	22	2 5	2		*Beans red kidney*	
Red kidney cnd or ckd	90	76 0	5 7	4	1 5	16 4	9	40	124	1 9			0	05	05	8	0	230	Cnd or ckd 1 cup	256
Others raw dry	338	11 5	21 4	1 6	3 9	61 6	4 0	163	437	6 9	1	1300	0	67	23	2 2	2	642	1 cup beans	190
Others bkd pork and molasses	125	70 0	5 8	3 0	2 0	19 2	9	56	113	2 1	480	210	30	05	04	5	2	325	Baked 1 cup	260
Others bkd pork and tomato sauce	113	71 7	5 8	2 1	2 0	18 4	1 0	41	113	1 8	400	140	80	05	04	5	2	295	Baked 1 cup	260

Lima green raw	128	66 5	7 5	8	1 7	23 5	1 5	63	158	2 3	1	680	280	21	11	1 4	32	96	Green raw ½ cup	75
Lima green ckd	95	74 9	5 0	4	1 4	18 3	2 0	29	77	1 7			290	14	09	1 1	15	152	Cooked 1 cup	160
Lima green cnd	71	80 9	3 8	3	1 5	13 5	1 3	27	73	1 7	310	210	130	04	04	5	8	176	Cnd 1 cup	249
Lima green frz	100	73 2	6 1	[illegible]	1 5	19 0	1 7	23	102	[illegible] 3	181	489	220	11	06	1 14	21	75	Frozen ⅓ cup	75
Lima dry	333	12 6	20 7	1 3	3 8	61 6	4 3	68	381	7 5	22 5	1758	0	48	18	2 0	2	610	Dry 1 cup	183
Snap green raw	35	88 9	2 4	2	8	7 7	1 4	65	44	1 1	9	300	630	08	11	5	19	26	Raw ¾ cup	75
Snap green ckd	2[illegible]	92 [illegible]	1 4	2	1 2	4 7	[illegible]	36	23	7			660	05	03	4	10	27	Cooked 1 cup	125
Snap green cnd	18	93 [illegible]	1 0	1	1 2	4 2	6	27	19	1 4	410	120	410	03	04	3	4	27	Canned 1 cup	125
Snap green frz	27	91 6	1 7	1	[illegible]	6 2	1 1	45	33	8	2	204	570	07	11	4	7	20	Frozen ¾ cup	75
Broccoli raw	29	89 9	3 3	2	1 1	5 5	1 3	130	76	1 3	16	400	3500	10	21	1 1	118	25	Raw 1 cup	120
Broccoli ckd	29	89 9	3 3	2	1 1	[illegible] 5	1 3	130	76	1 3			3400	07	15	8	74	44	Cooked 1 cup	150
Broccoli frz	30	90 2	3 4	3	8	5 3	1 1	61	63	8	16	214	2850	07	13	6	62	36	Frozen 1 cup	120
Cauliflower raw	25	91 7	2 4	2	8	4 9	9	22	72	1 1	24	400	90	11	10	6	69	31	Raw 1½ cup	125
Cauliflower ckd	25	91 7	2 4	[illegible]	8	4 9	9	22	72	1 1			90	06	08	5	28	30	Cooked 1 cup	120
Cauliflower frz	22	92 7	2 1	2	[illegible]	4 3	9	18	45	6	11	234	33	06	06	4	55	27	Frz 1¼ cup	125
Corn sweet raw	92	73 9	3 7	1 2	7	20 5	8	9	120	5	3– 4	240–370	390	15	12	1 7	12	92	1 ear 8 long	100
Corn sweet ckd	85	75 5	2 7	7	9	20 2		5	52	6			390	11	10	1 4	8	85	Ckd 1 ear 5	140
Corn sweet cnd	67	80 5	2 0	5	9	16 1	8	4	51	5	205	200	200	03	05	9	5	140	Cnd 1 cup	116
Cucumbers raw	12	96 1	7	1	4	2 7	5	10	21	3	9	2[illegible]0	0	03	04	2	8	6	Raw 6 ⅛ w slices	50
Egg plant raw	24	92 7	1 1	2	5	5 5	9	15	37	4	9	190	30	04	05	6	5	60	2 slices	250
Lentils dry split	339	12 2	24 0	1 3	2 2	60 4	1 7	34	293	7 4	3	1200	570	56	24	2 2	5	204	Lentils ½ cup	60
Mushrooms raw	16	91 1	2 4	3	1 1	4 0	9	9	115	1 0	5	[illegible]20	0	10	44	4 9	5	8	½ cup diced	50
Mushrooms canned	11	93 0	1 4	2	1 0	3 7		7	90	8	400	1[illegible]0	0	02	25	2 0		28	Canned 1 cup	244
Okra cooked	32	89 8	1 8	2	8	7 4	1 0	82	62	7	1	220	740	06	06	8	20	28	Cooked 8 pods	85
Peas green raw	98	74 3	6 7	4	9	17 7	2 2	22	122	1 9	1	370	680	34	16	[illegible] 7	26	74	Peas green ½ cup	75
Peas green cooked	70	81 7	4 9	4	9	12 1	2 2	22	122	1 9			720	25	14	2 3	15	111	Cooked 1 cup	60
Peas green cnd	68	82 3	3 4	4	1 0	12 9	1 4	25	67	1 8	270	96	510	11	06	1 0	8	145	Canned 1 cup	60
Peas green frz	83	80 3	5 7	4	8	12 9	1 8	24	92	2 2	160	153	670	33	10	1 9	17	124	Frozen 1 cup	150
Peas dry split	344	10 0	24 5	1 0	2 8	61 7	1 2	33	268	[illegible] 1	42	880	370	77	[illegible]8	3 1	2	689	Dry split 1 cup	200
Peppers green raw	25	92 4	1 2	2	5	5 7	1 4	11	25	4	6	170	630	04	07	4	120	16	1 medium pepper	76
Pumpkin raw	31	90 [illegible]	1 2	2	8	7 3	1 3	21	44	8	6	450	3400	05	08	6	8	37	Raw ¾ cup	120
Pumpkin cnd	33	90 [illegible]	1 0	3	6	7 9	1 2	20	36	7	2	240	3400	0[illegible]	06	5		76	Canned 1 cup	228
Soybeans dry	331	7 [illegible]	34 9	18 1	4 7	34 8	5 0	227	5[illegible]6	8 0	4	1900	110	1 07	31	2 3	Tr	695	Dry 1 cup	210
Soybean flour med fat	264	9	42 5	6 5	4 8	37 2	2 6	244	610	13 0	1	1700	110	82	34	2 6	0	232	1 cup soy flour	88
Soybean sprouts raw	46	86 3	6 2	1 4	8	5 3	8	48	67	1 0			180	23	20	8	13	[illegible]0	Raw 1 cup	107
Squash summer raw	16	95 0	6	1	4	3 9	[illegible]	15	1[illegible]	4	[illegible]	1[illegible]0	260	05	09	8	17	40	1½ cup diced	250
Squash summer frz	16	9[illegible] 0	6	1	4	3 9	[illegible]	15	15	4			2[illegible]0	04	08	7	11	34	Ckd diced 1 cup	210
Squash winter raw	38	88 6	1 [illegible]	3	8	8 8	1 4	19	28	6	3	240	4950	05	1[illegible]	5	8	95	1½ cup diced	2[illegible]0
Squash winter ckd	47	85 7	1 9	4	1 0	11 0	1 8	24	35	8			6190	05	15	6	7	97	Mashed 1 cup	205
Succotash frz	97	60 3	4 5	4	8	21 4	9	15	90	1 2	73	279	167	11	06	1 5	7	205	¾ cup ckd	210

TABLES OF FOOD COMPOSITION (*Continued*)

Constituents of 100 G of Edible Portion

Name	Proximate Composition							Minerals					Vitamins					Average Portion		
	Calories	Water g	Protein g	Fat g	Ash g	Total Carbohydrates g	Crude Fiber g	Calcium mg	Phosphorus mg	Iron mg	Sodium mg	Potassium mg	A I U	B_1 mg	B_2 mg	Nicotinic Acid mg	C mg	Total Calories	Measure	Wt in g
FLOWER FRUIT AND SEED VEGETABLES—(*Continued*)																				
Tomatoes raw	20	94 1	1 0	3	6	4 0	6	11	27	6	3	230	1100	06	04	5	23	30	1 med 2 × 2½"	150
Tomatoes canned	19	94 2	1 0	2	7	3 9	4	11	27	6	18	130	10.0	06	03	7	16	46	Canned 1 cup	242
Tomato ketchup	98	69 5	2 0	4	3 6	24 5	4	12	18	8	1300	800	1880	09	07	2 2	11	17	1 tbsp ketchup	17
Tomato purée cnd	36	89 2	1 8	5	1 3	7 2	4	11	37	1 1			1880	09	07	1 8	28	90	1 cup purée	249
MISCELLANEOUS																				
Cola beverages	46	88				12					1	52						83	6 oz cola	180
Ginger ale	35	91				9					8	6						63	6 oz ginger ale	180
Popcorn	386	4 0	12 7	5 0	1 6	76 7	2 2	11	281	2 7	2000	240	0	39	12	2 2	0	54	1 cup popped	14
Potato chips	544	3 1	6 7	37 1	4 0	49 1	1 1	30	152	1 9	340	880	50	18	11	3 2	11	108	10 medium 2"	20
Yeast baker s compressed	86	70 9	10 6	4	2 4	13 0	3	25	605	4 9	4	300	0	45	2 07	28 2	0	24	1 oz yeast	28
Yeast brewer s dry	273	7 0	36 9	1 6	7 9	37 4	8	106	1893	18 2	150	1700	0	9 69	5 45	36 2	0	22	1 tbsp yeast	8

BEVERAGES

Tea and Coffee—The physiological influence of these beverages is due to their caffeine content, which has a stimulating effect on the higher centers of the brain In moderation, neither is harmful, but if taken in excess, toxic effects of caffeine may appear, such as irritability insomnia, and tachycardia Therefore their intake should be restricted in cardiac conditions and in hyperthyroidism, when the heart is already overstimulated The partaking of excessive quantities of tea particularly if the leaves have been stewed for a long time, is a potent cause of dyspepsia

Tea, coffee, cocoa and chocolate all have a high purine content and their use is to be restricted in gout

Alcohol—Pure alcohol has an energy value of 200 calories per ounce The body can completely oxidize only limited quantities of alcohol, the maximum being 10 cc of pure alcohol per hour the amount contained in about one ounce of whiskey No advantage is gained by administering alcohol in larger doses while considerable harm may result from its cumulative action In medical practice half to one ounce of whisky or brandy 3 or 4 times daily has been found to be an adequate dose In small amounts it can be burned in place of quantities of carbohydrate or fat of equal caloric value Accordingly, any intake of wines or spirits of high alcohol content must be considered when the caloric value of the diet is of importance, as in obesity and diabetes The energy intake derived from alcoholic beverages is not of course due entirely to their alcoholic content, since sweet wines contain unfermented sugar, and beer and other malt liquors contain carbohydrate from the malt

Beer, cider and stout contain from 4 to 5 per cent of alcohol, light table wines contain 8 to 12 per cent, the fortified wines like port and sherry contain about 20 per cent while spirits such as gin whisky rum and brandy contain 40 to 50 per cent

The liqueurs contain 20 to 50 per cent of alcohol but this is of little importance in view of the small amount taken On the other hand, their sugar content is as high as 30 per cent and a liqueur glassful contains about 5 grams of carbohydrate—*a fact to be remembered* when a diabetic patient asks advice regarding alcoholic beverages

ALCOHOLIC BEVERAGES

		Calories
Beer and ales	1 8-oz glass	115
	1 12 oz bottle	172
Dry wines such as claret, sauterne Tokay, Burgundy, champagne	1 4-oz wine glass	80
Distilled spirits such as whiskey gin rum, brandy	1 1-oz glass	80
	1 jigger	119
Cocktails average	1 4-oz glass	185
Mint juleps	1 average	258
Eggnog	1 tall glass	422

Appendix

Weight and Capacity Measures and Their Equivalents

Measure	Equivalent
4 ounces	1/4 pound
16 ounces	1 pound
80 minims	1 teaspoonful
3 teaspoonfuls	1 tablespoonful
4 tablespoonfuls	1/4 cup
8 tablespoonfuls	1/2 cup
16 tablespoonfuls	1 cup
1 gill	1/2 cup
2 cups	1 pint or 16 fluid ounces
4 cups	1 quart
4 quarts	1 gallon
8 quarts	1 peck

Measure	Equivalent
1 gram carbohydrate	4 calories
1 gram protein	4 calories
1 gram fat	9 calories
1 tablespoon	4 drams, 15 cubic centimeters
1 teaspoonful	1 dram, 4 cubic centimeters
29.6 cubic centimeters	1 fluid ounce
28.35 grams	1 ounce
1 kilogram (1000 grams)	2.2 pounds
473.2 cubic centimeters	1 pint
100 grams	3.5 ounces
100 cubic centimeters	3.4 fluid ounces
1 liter (1000 cubic centimeters	33.8 fluid ounces (2.1 pints approximately)

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